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SLEEP AND ITS TIMING – LONGITUDINAL AND CROSS-SECTIONAL ASSOCIATIONS WITH COGNITIVE PERFORMANCE AND HEALTH IN YOUTH

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ACADEMIC DISSERTATION

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ABSTRACT

Sleep duration, quality, and timing have been identified as factors which are associated with neurocognitive functioning, health, and overall well-being – often reciprocally. Studies in healthy, typically developing children and adolescents are sparse, and, typically, use either self-reports or parent-reported measures of habitual sleep, or rely on experimental sleep restriction settings which enable estimating the effects of insufficient sleep on, for instance, memory or executive functions.

The goals of this study included investigating typical, non-restricted sleep and the domain-specific associations it has with health and cognitive performance over a developmental span from middle childhood to early adulthood. Specifically, (1) identifying the cross-sectional associations between neurocognitive functioning and habitual sleep duration and sleep quality in early adolescence, and (2) studying the sleep behaviour associated with young adults' executive functioning. Additionally, the goals included (3) studying the longitudinal associations between naturally occurring sleep and lipid profile in early adolescence, and, finally, (4) differentiating the developmental trajectories of sleep timing from middle childhood to adolescence from a circadian preference perspective.

The participants came from two population-based cohorts. The children and adolescents came from a community-based GLAKU cohort, and the young adults came from the Arvo Ylppö Longitudinal Study (AYLS). The original GLAKU cohort (Glycyrrhizin in Licorice) was set up to investigate blood pressure and liquorice consumption during pregnancy. The cohort consisted of 1049 children born in 1998; 413 were invited for a follow-up in 2006; 920 in 2009-2011, and, 279 in 2015. Of the invited, 78 % participated in 2006. In 2009-2011, 49 % participated, and, in 2015, 71 % of the invited participated. In this study, 105 children were included in the analyses at age 8.1 years, 354 were included at mean age 12.3 years, and all in all 111 adolescents part of the longitudinal analyses with data from 2006, 2009-2011, and 2015 at age 16.9 years.

The AYLS participants were born in Helsinki in 1985-1986 (original sample n=2193). 1913 could be invited to a follow-up study in 2009-2011, and 52 % participated. Our sample included only full-term participants with sleep measurements, resulting in 512 young adults at the age of 25.3 years.

All the studies in this thesis were done using actigraphs with piezoelectric accelerometers, which provide objective sleep measures based on movement. Using actigraphy alongside sleep diaries, it is possible to detect sleep duration and timing. Additionally, the adolescents reported their own preference for morningness or eveningness at the age of 16.9 years.

Cognitive performance was evaluated in three overall domains in early adolescence: intelligence, executive function, and memory. Young adults' executive functioning was evaluated using both performance-based tests and a self-report for estimating the trait-like features of executive functioning. Children's lipid levels, which are considered to be a marker for future cardiovascular health, were analysed from fasting serum samples and the associations between sleep and high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides were investigated.

We found that neither intelligence nor memory test performances were associated with naturally occurring sleep. During early adolescence, especially boys' shorter sleep duration was associated with poorer performance in tests evaluating executive functioning. We found similar results in young adults, but also found that later sleep timing and regularity were associated with weaker trait-like executive functioning.

Longitudinal analyses revealed that girls' longer sleep in middle childhood was associated with a more beneficial lipid profile in early adolescence. These findings were also present in cross-section, but not as profoundly. We also analysed the sleep patterns of different circadian preference phenotypes longitudinally, and found that those adolescents with a preference for morningness differed from others in sleep timing already at age 8.

Based on these findings, objectively measured sleep and its timing have domain-specific associations with cognitive performance. These associations are present in both children and adults, but, in earlier development, boys' executive functioning may be more vulnerable. The longitudinal trajectories of sleep may be particularly significant regarding health outcomes: girls' lipid profiles showed a more profound association with accumulating sleep habits than with sleep measured cross-sectionally. The longitudinal pathways of sleep timing are also a potential threat for future health, as eveningness and later circadian rhythm present a risk for various adverse outcomes.

TIIVISTELMÄ

Unen kesto, laatu, ja ajoitus ovat keskeisesti yhteydessä neurokognitiiviseen suoriutumiseen, terveyteen ja yleiseen hyvinvointiin – usein vastavuoroisesti. Tutkimukset, joissa tutkimuskohteina on terveitä, tyypillisesti kehittyneitä lapsia ja nuoria, ja joissa on käytetty objektiivisia mittausmenetelmiä, ovat verrattain harvinaisia. Tyypillisesti unen mittaamisen menetelminä on käytetty joko itseraportointia tai huoltajan kirjaamia lukemia. Toisaalta myös kokeelliset asetelmat ovat yleisiä: niissä unen kestoa rajoitetaan, jolloin voidaan arvioida, miten liian lyhyeksi jäävä yöuni vaikuttaa vaikkapa muistiin tai toiminnanohjaukseen.

Tässä väitöskirjatutkimuksessa selvitettiin, kuinka tyypillinen uni on yhteydessä terveyteen ja kognitiiviseen suoriutumiseen ihmisen eri kehitysvaiheissa keskilapsuudesta varhaisaikuisuuteen. Keskeisenä tavoitteena on erilaisten kognitiivisten toimintojen erotteleminen siinä mielessä, miten voimakkaasti ne ovat yhteydessä tavanomaisesti esiintyvään heikkoon tai riittämättömään uneen. Erityisesti tavoitteena oli (1) tarkastella poikittaistutkimuksena neurokognitiivisen toiminnan ja tavanomaisen unen keston ja laadun yhteyttä nuoruudessa, sekä (2) nuorten aikuisten toiminnanohjauksen yhteyksiä unen määrään ja ajoitukseen. Lisäksi tämän tutkimuksen pyrkimyksenä oli (3) tarkastella pitkittäisyhteyksiä tavanomaisen unen ja lipidiprofiilin välillä varhaisnuoruudessa, sekä (4) jäljittää unen ajoituksen kehityspolkuja keskilapsuudesta nuoruuteen vuorokausirytmin aamu- tai iltatyyppi -luokittelun näkökulmasta. Monesta tutkimuksesta on saatu näyttöä siihen suuntaan, että myöhäinen vuorokausirytmi on terveysriski.

Osallistujat ovat peräisin kahdesta väestöpohjaisesta kohortista: lapset ja nuoret osallistujat ovat GLAKU-tutkimuksesta, ja nuoret aikuiset ovat Arvo Ylppö Longitudinal Study (AYLS) – tutkimusaineistosta. GLAKU-seurantatutkimukset ovat jatkoa vuoden 1998 verenpainetta ja äidin raskaudenaikaista lakritsinsyöntiä tarkastelleelle tutkimukselle, johon osallistui alun perin 1049 Helsingissä syntynyttä lasta. Vuonna 2006 kutsuttiin 413 lasta osallistumaan seurantaan; heistä osallistui 78 %; vuosina 2009–2011 kutsuttiin 920, joista osallistui 49 %, ja vuonna 2015 kutsuttiin 279 joista osallistui 71 %. Tässä tutkimuksessa mukana oli 105 lasta keskimäärin 8.1-vuotiaana, 354 varhaisnuorta keskimäärin 12.3-vuotiaana, ja kaiken kaikkiaan 111 nuorta, jotka olivat mukana kahdessa aiemmassa seurannassa, ja myös 16.9-vuotiaana. AYLS –tutkimuksessa oli alun perin mukana 2193 vuonna 1985–1986-syntynyttä osallistujaa, joista seurantatutkimukseen kutsuttiin 1913 nuorta aikuista vuosina 2009–2011. Heistä osallistui 52 %, joista täysiaikaisina syntyneitä oli 512, keskimäärin 25.3-vuotiasta, jotka otettiin mukaan tähän tutkimukseen.

Unta mitattiin kaikissa tutkimuksen vaiheissa objektiivisesti pietsosähköisillä kiihtyvyysantureilla niin lapsilla kuin aikuisillakin.

Kiihtyvyysanturit eli aktigrafit antavat unipäiväkirjojen ohessa käytettyinä luotettavaa tietoa unen määrästä ja ajoituksesta käden liikkeiden perusteella. Lisäksi nuoret arvioivat 16.9-vuotiaina vuorokausirytminsä ilta- tai aamutyyppisyyttä.

Varhaisnuorten neurokognitiivista suoriutumista arvioitiin tutkimuksessa kolmen eri testialueen suhteen: älykkyyden, toiminnanohjauksen sekä muistin osalta. Nuorten aikuisten tutkimuksessa keskityttiin toiminnanohjauksen itse raportoituun arvioon, sekä testisuoriutumiseen. Lisäksi lasten paastoveren lipidiarvoista tarkasteltiin HDL- ja LDL-kolesteroliarvoja sekä triglyseridejä, joiden voidaan ajatella mittaavan riskitekijöitä sydän- ja verisuoniterveyden suhteen.

Poikittaistutkimuksessa selvisi, että varsinkin poikien lyhyt ja levoton uni oli yhteydessä heikompaan suoriutumiseen toiminnanohjaustesteissä, mutta ei älykkyys- tai muistitestien tulokseen. Kun tarkasteltiin nuoria aikuisia, lyhyt tai epäsäännöllinen uni oli yhteydessä heikompaan toiminnanohjauksen testisuoriutumiseen, ja myöhäisempi tai epäsäännöllinen unirytmi taas heikompaan toiminnanohjauksen itsearvioon. Nämä löydökset tulivat esiin sekä miehillä että naisilla.

Pitkäkestoisesti tarkasteltuna tutkimuksessa kävi ilmi, että lyhyt unen kesto ja riittämätön arjen uni keskilapsuudessa olivat yhteydessä varhaisnuoruuden haitallisemmaksi arvioituun lipidiprofiiliin tyttöjen keskuudessa. Sama tulos toistui poikittaistarkastelussa, mutta pitkittäiset yhteydet vaikuttivat voimakkaammin. Unen pitkittäistarkastelussa kävi myös ilmi, että unen ajoitus 8-vuotiaana poikkeaa niillä lapsilla, jotka yhdeksän vuotta myöhemmin raportoivat olevansa aamutyyppisiä vuorokausirytmiltään.

Aiemmat tutkimukset eivät ole raportoineet tyypillisen, objektiivisesti mitatun unen keston, laadun, ja ajoituksen yhteyksiä kognitiiviseen suoriutumiseen testien eri osa-alueilla. Näyttäisi siltä, että lyhyempi unen kesto on yhteydessä välittömään toiminnanohjauksen testisuoriutumiseen, kun taas unen myöhäisempi ajoitus liittyy itse raportoituun toiminnanohjauksen kokonaisarvioon.

Kun tarkastellaan unta ja terveysriskejä pitkittäin, tässä tutkimuksessa löydettiin uneen liittyvien tekijöiden kumuloitumista ajan myötä: tyttöjen pidempi ja säännöllisempi uni suojaa haitallisemmaksi arvioidun lipidiprofiilin muodostumiselta. Keskilapsuuden aikaisempi vuorokausirytmi voi osaltaan vähentää myöhempää iltatyypiksi kasvamisen riskiä.

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There are two kinds of success: either you get it right immediately, or you work your way through a sum of numerous failures and mistakes. Getting this PhD thesis printed and defended is mostly the slower kind of success, but it was fun while it lasted.

On the 1st of June, 2018, it will be 1766 days since I started working in the developmental psychology research group. This equals 42384 hours, of which I have probably slept approximately 13245 hours. My work contract states that I should work 1600 hours every year (or, 1624 hours from 2017 onwards), so, over the past 4 years and 10 months this adds up to 7777 hours of work; less than 60 % of the time I've spent sleeping. Based on these figures, it is evident that sleep has played a big part in the birth of this thesis, both in theory and in practise. Therefore: first and foremost I would like to acknowledge sleep as the biggest contributor to this thesis. Thank you for serving me well. I couldn't have done this without you.

Not far from this acknowledgement is the role of my first supervisor, professor Anu-Katriina Pesonen, whose office door has always been open for me to bring in any worries, and who has always responded to my questions as soon as humanly possible. I have understood that the PhD process is seldom fun, but based on my own experience I would not know this. Thank you.

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CONTENTS

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

I Kuula, L., Pesonen, A. K., Martikainen, S., Kajantie, E., Lahti, J., Strandberg, T., Tuovinen, S., Heinonen, K., Pyhälä, R., Lahti, M. & Räikkönen, K. (2015). Poor sleep and neurocognitive function in early adolescence. *Sleep Medicine*, 16(10), 1207–1212.

II Kuula, L., Pesonen, A. K., Kajantie, E., Lahti, J., Andersson, S., Strandberg, T., & Räikkönen, K. (2016). Sleep and lipid profile during transition from childhood to adolescence. *The Journal of Pediatrics*, 177, 173–178.

III Kuula, L., Pesonen, A.K., Heinonen, K., Kajantie, E., Eriksson, J.G., Andersson, S., Lano, A., Lahti, J., Wolke, D. & Räikkönen, K. (2018). Naturally occurring circadian rhythm and sleep duration are related to executive functions in early adulthood. *Journal of Sleep Research*, 27(1), 113–119.

IV Kuula, L., Pesonen, A. K., Merikanto, I., Gradisar, M., Lahti, J., Heinonen, K., Kajantie, E. & Räikkonen, K. (2017). Development of Late Circadian Preference: Sleep Timing from Childhood to Late Adolescence. *The Journal of Pediatrics*, 194: 182–189.

The publications are referred to in the text by their roman numerals.

ABBREVIATIONS

ANCOVA analysis of covariance
AYLS Arvo Ylppö Longitudinal Study
B Regression coefficient
BMI Body mass index
BRI Behavioral Regulation Index
BRIEF-A Behavior Rating Inventory of Executive Function
CI Confidence interval
CPT Conners' Continuous Performance Test II
EEG Electroencephalogram
EF Executive function
EMG Electromyogram
EOG Electro-oculogram
GEC Global Executive Composite
HDL-C High-density lipoprotein cholesterol
IQ Intelligence quotient
LDL-C Low-density lipoprotein cholesterol
MD Mean difference
MEQ Morningness-Eveningness questionnaire
MI Metacognition Index
N1 Stage 1
N2 Stage 2
N3 Stage 3
NEPSY 2 Developmental Neuropsychological Assessment for children 2
NREM Non-rapid eye movement
PDS Pubertal Development Scale
REM Rapid eye movement
SCN Suprachiasmatic nucleus
SD Standard deviation
SE Sleep efficiency
SES Socio-economic status
SHY Synaptic homeostasis hypothesis
TC Total cholesterol
TGs Triglycerides
TIB Time in bed
TST Total sleep time
TMT Trail making test
WASO Wake after sleep onset
WCST Wisconsin Card Sorting Task
WISC Wechsler Intelligence Scale for Children III

1 INTRODUCTION

Sleep is extremely time-consuming, and as a result, we never seem to get enough of it. Sometimes insufficient sleep is a choice we make due to external reasons, but sometimes it results inadvertently from environmental, somatic, or mental problems.

Despite advances in the field of sleep medicine, sleep continues to be one of the great mysteries in life. We are only beginning to understand how important sleep is, and in how many ways it benefits the body and the mind. Sleep deprivation studies have revealed many unfavourable causes from lack of sleep, and, similarly, insufficient sleep and sleep disorders are associated with adverse outcomes (Aho et al., 2016; Bayon, Leger, Gomez-Merino, Vecchierini, & Chennaoui, 2014; Cespedes et al., 2014; Durmer & Dinges, 2005; Goel, Basner, Rao, & Dinges, 2013; Killgore et al., 2008; Trivedi, Holger, Bui, Craddock, & Tartar, 2017). These include neurocognitive dysfunction, psychiatric symptoms, cardiovascular disease, obesity, as well as higher risk for accidents and injuries. Modern life seems to raise the prevalence of short or insufficient sleep in youth (Gradisar, Gardner, & Dohnt, 2011), but not in adulthood (Bin, Marshall, & Glozier, 2013). As youth is also a time of higher prevalence of the onset of different mental disorders, and a crucial time for education pathway selection, this time period is sensitive as a foundation for future health and well-being. The nocturnal elements of this developmental stage, i.e. overnight habitual sleep, cannot be overlooked as one core element in building this foundation.

2 REVIEW OF THE LITERATURE

2.1 SLEEP: DEFINITIONS AND MEASURES

Sleep is essential, but not fully understood. Despite huge advances in methodologies, it is still unknown why we need to sleep approximately a third of our lives. Recent methodological advances have shed light on the complexities involved in determining sleep need and sleep behaviour: detailed information on different brain structures involved in sleep-wake regulation is now available thanks to accurate imaging equipment. Additionally, animal studies and the development of optogenetics (Weber et al., 2015) and targeted genome modification (such as CRISPR-CAS9) (Tsuchiya et al., 2015) enable investigating the precise genetics involved in sleep stages and circadian regulation in extreme detail. As a similar advance in measurements, recent technologies have enabled data collection in great volumes: alongside the development of commercial or consumer-aimed accelerometers the measurement of sleep has become an everyday observation similar to weighing oneself or measuring body temperature. Even though these advancements have given research detailed information of both mechanisms and common behaviours relating to sleep, the functions, causes and consequences of sleep remain partially unsolved. As we strive to understand and measure sleep, a clear definition is needed to ensure which phenomenon is under scrutiny: is sleep physical rest, a change in consciousness, or is it a specific state in the brain, or do we need to consider all these aspects while investigating sleep-related phenomena. Whenever we measure sleep, the theoretical assumptions involved must be defined in order to understand the phenomenon accurately. The next paragraphs will define the theoretical setup of sleep relevant to this thesis.

2.1.1 WHAT IS SLEEP?

All thus far observed animals sleep, and, in more detail, all cells seem to produce some patterns of activity and rest (Cirelli & Tononi, 2008; Vyazovskiy & Harris, 2013). However, sleep is different from rest, and different measures of sleep may serve very different functions across different species (Siegel, 2008). Sleep can be defined from several viewpoints, even if we only observe mammalian sleep. From a behavioural point of view, sleep is a reversible state of disengagement and unresponsiveness to the environment. This state can be observed from the

outside as closed eye lids, lack of movement, a change in breathing, and, general quietness. While from the outside observer this may seem a unitary state, sleep consists of different levels, or, stages which can be either lighter or deeper. Subjectively, sleep is observed as a shift in consciousness, which may furthermore alter when sleep stages change. However, behavioural changes are neither necessary nor sufficient in defining sleep: different levels of consciousness, including unconsciousness, may have similar qualities. When estimating sleep based on behavioural change, a multi-faceted approach may produce the most reliable result: lack of movement is not a sufficient determinate of sleep, but becomes reliable when combined with a subjective report of falling asleep.

Besides the behavioural, or, observational viewpoint, sleep can also be defined through several physiological parameters. Electrophysiological measurements have long been considered the most accurate in detecting sleep timing and stage, with first reported measurements of different sleep stages in the 1930s (Loomis, Harvey, & Hobart, 1937) and rapid eye movement (REM)/ non-REM (NREM) differentiation in the 1950s (Aserinsky & Kleitman, 1953; Dement & Kleitman, 1957). Sleep in different stages is manifested as distinguishable patterns in electric activity. In addition to the general division between REM and NREM, in humans, sleep stages can be further separated into Stage 1 (N1), Stage 2 (N2), Stage 3 (N3), and up until 2007, Stage 4 sleep. Of all the stages, REM (also called paradoxical sleep due to its electrophysiological, and sometimes partially physical similarity to being awake) is the most dynamic one: eyes move rapidly, and if a person is woken up during this phase, they will often recall experiencing vivid, life-like dreams. Stages 3 (and 4) constitute slow wave sleep (SWS), which is considered the deepest and most restorative sleep. Some studies have indicated a relationship between the amount of SWS, and sleep debt (Boonstra, Stins, Daffertshofer, & Beek, 2007): sleep debt is paid back primarily in SWS while the amount of sleep in other stages gets suppressed.

The different stages of sleep can only be identified reliably using polysomnography (PSG). PSG typically includes at least electroencephalogram (EEG), electromyogram (EMG), and electro-oculogram (EOG), and it allows accurate estimation of different sleep stages by attaching electrodes to the scalp and skin in order to detect electric activity, muscle tonus and eye movements.

The sleep-wake regulation system has several hierarchies, which all play a part in regulating sleep onset, maintenance, and sleep timing. Borbely (Borbely, 1982) outlined a two-process-model with two independent mechanisms regulating sleep: Process S and Process C. These theoretical processes build on different systems, which interact and thus produce sleep and wake rhythms. Ever since lesion studies (Moore & Eichler, 1972; Stephan & Zucker, 1972) in 1972 revealed that the suprachiasmatic nucleus (SCN) contains tissue which enables circadian rhythmicity, the investigation of

neural correspondents responsible for sleep regulation has been exponential. On a molecular level, the circadian process links positive and negative feedback mechanisms of circadian genes, and the proteins which are expressed within the SCN cells. In addition to behavioural and physiological definitions of sleep, brain circuitry and neurotransmitters (e.g., gamma-aminobutyric acid, galanin, melanin-concentrating hormone, and orexin/hypocretin) relating to sleep onset and maintenance have been identified. Neural representations of sleep states typically require invasive measurements, thus having limited applicability in everyday definitions of sleep and wake.

Process S, or the homeostatic process, represents the build-up of sleep pressure as a function of time spent awake. The homeostatic process has a physiological correspondent: a recent study (Pimentel et al., 2016) reported finding the sleep-wake –switch, which responds to homeostatic sleep need. Within the dorsal fan-shaped body of the central complex, there is a cluster of neurons which are electrically active during sleep, and silent during wakefulness. Within these neurons, there is an ion channel (now named 'Sandman') that is kept inside the sleep-control neurons when they are electrically active (Pimentel et al., 2016).

Process C, or the circadian timing process, regulates the timing of sleep and wakefulness over approximately 24 hours, waxing and waning in a wave-like rhythm. While Process S is greatly affected by prior wakefulness, Process C is not dependent on previous sleep. However, several other factors contribute to Process C, and the onset of melatonin which is a key hormone in circadian processes. At least light (van Maanen, Meijer, van der Heijden, & Oort, 2016), temperature (Refinetti, 2015), food (Duffy & Dijk, 2002), exercise (Richardson, Gradisar, Short, & Lang, 2016), and possibly other external cues set a pace in circadian rhythms.

When considering all the neural, environmental, social, and behavioural aspects of mammalian sleep, it is safe to say there are many pieces in the puzzle. A bio-mathematical model which includes fatigue, alertness, and implications of the relationship between the two processes has been proposed (McCauley et al., 2013). For the purposes of practicality, we may simplify the definition of sleep as a behavioural state of quietness with corresponding brain activity typical for one of the sleep stages.

2.1.2 WHY DO WE SLEEP?

Sleep endeavours a great percentage of human life (estimates 30-40 %), yet no single explanation for this has been found. It is likely that sleep serves several functions; research suggests that sleep serves purposes which relate to both physical and mental abilities as well as well-being.

Physical functions of sleep are likely to relate to those changes that occur during night-time sleep, though these are not necessarily related to sleep per se, but may be partially explained by physical rest or time of day (i.e. night). These changes typically occur only in NREM sleep (sometimes called quiet sleep), and include a drop in core body temperature and blood pressure, overall reduction in heart rate, decreased breathing rate, lowered kidney function activity and production of urine decreases. However, these changes are very different in REM sleep, which may be more similar to wakefulness than sleep. During REM the muscle tonus decreases, but the physiological functions may vary in a similar way as when we are awake. For instance brain energy consumption as measured by oxygen and glucose metabolism can be even higher during REM than during wakefulness; accordingly, REM sleep is sometimes also referred to as active sleep. (Mary A Carskadon & Dement, 2005)

Based on the changes which occur during sleep, it has been suggested that one function of mammalian sleep might be adaptive inactivity or energy conservation (Siegel, 2009), or, to restore the brain and body after activities during the waking hours (Sassin et al., 1969). Other suggested functions of sleep have included both cleaning of metabolite residuals in the central nervous system (Xie et al., 2013) and the metabolism of extracellular neurotransmitter concentrations (such as adenosine) (Porkka-Heiskanen, 1999). Preventing connectivity changes may also be one function: a recent theory suggests that sleep recalibrates homeostatic and associative synaptic plasticity, which is believed to be the neural basis for adaptive behaviour (Tononi & Cirelli, 2014). This synaptic homeostasis hypothesis (SHY) relating to synaptic strength is assumed to explain some of the associations found between cognitive function and sleep (Cirelli & Tononi, 2015). The potential mechanism relates to changes in plasma brain-derived neurotrophic factor (Kuhn et al., 2016), but other mechanisms have also been proposed too, such as synaptic remodelling through Homer1a, which works as molecular integrator through the wake-promoting noradrenaline and sleep-promoting adenosine (Diering et al., 2017). During sleep, noradrenaline levels decline, allowing Homer1a to move to excitatory synapses, drive synapse weakening, which may enable the consolidation of memory. Furthermore, previous studies have shown specific traits in human sleep EEG to demonstrate this effect on an electroencephalogram level: sleep spindles are thought to play a key role in the plasticity of the brain (Clawson, Durkin, & Aton, 2016).

Besides specific physical functions, research in mammals has recognized the importance of sleep from a cognitive viewpoint. Remembering and forgetting are active processes which are greatly aided by sleep (Diekelmann, Wilhelm, & Born, 2009). Memory consolidation depends on the different stages of sleep; it is hypothesized that N2 and N3 sleep deliver the material to be memorized into the hippocampus area, where it is then temporarily stored and further transferred to the neocortex for long-term

storage. The association between sleep and memory is discussed in more detail in 2.2.1.2. Noteworthy, sleep (and its memory consolidative properties) also plays a part in depression and anxiety: the relationship is bi-directional and has been studied extensively (Lovato & Gradisar, 2014; Zhai, Zhang, & Zhang, 2015). Also, sleep after surviving traumatic experiences may influence the outcome and prognosis – this is likely to be a result of memory consolidation (Pace-Schott, Germain, & Milad, 2015).

2.1.3 HOW DO WE SLEEP?

Sleep has many parameters which may fluctuate depending on several reasons. The most studied, and perhaps the most evident, is sleep duration. The length of night-time sleep is the proxy for estimating sufficient sleep, and typically the one that is enquired in self-reports and questionnaires. Duration may be measured as time in bed (TIB), which includes the entire period a person tries to sleep. In some studies a more specific measure of sleep duration is named "assumed sleep", which excludes sleep latency (i.e. the time it takes to fall asleep). A further measure, "actual sleep duration", is sometimes reported; it is similar to assumed sleep, but excludes micro-arousals and small awakenings, which can be derived from objective measures of sleep. Typically, all measures of sleep duration give estimations whether a person gives sufficient time for their sleep. However, it does not take into account sleep quality, timing, regularity, sleep debt, or, sleep architecture, which all play a part in sleep behaviour and its consequences.

In addition to sleep duration (or quantity), sleep quality can be used in estimating the associations sleep has with bodily abilities and functions. Depending on the studied person or population, sleep quality can be measured using questionnaires or objective measures. Typically sleep quality as measured by questionnaires is operationalized by calculating the severity, frequency and duration of dyssomnia symptoms (such as narcolepsy, idiopathic hypersomnia, insomnia, restless legs syndrome, and sleep apnoea) (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). Additionally, parasomnias (such as sleepwalking, sleep terrors, sleep bruxism, nightmares or abnormal movements) may perish sleep quality. Finally, the resulting sleepiness or symptomology can also be used as a measure of sleep quality in questionnaires. Besides questionnaire measures of sleep quality, objective methodology provides specific information on arousals or movements during sleep – these tap on poor quality within normal variation of sleep, or dyssomnias or parasomnias. Sleep efficiency percentage and "wake after sleep onset" (WASO) are the most commonly reported measures of sleep quality in objective measurements.

Measuring sleep duration and quality may provide sufficient information on sleep in many cases. However, sleep timing and regularity also play a central part in the health- and performance-related outcomes of sleep (Miller, Lumeng, & LeBourgeois, 2015). Specifically, sleep timing and circadian rhythms modulate, or control daily physiological patterns. Circadian clock mechanisms in neurological pathways play a key role in several developmentally central functions (Van Someren et al., 2015), which are likely to, in turn, reflect on both physiological and cognitive processes. Circadian rhythms partially depend of individual circadian preferences, and play an important part in sleep behaviour, daily functioning, and health (Roenneberg et al., 2007; Roenneberg, Wirz-Justice, & Merrow, 2003).

In relation to sleep-wake-rhythms, there is a neighbouring concept of circadian preference. Circadian preference is a behavioural trait-like quality with some genetic foundations (Jones et al., 2016) but also a social and habitual component (Mistlberger & Skene, 2004). The core circadian preference concepts of "morningness" and "eveningness" were internationally introduced in 1976, and the associated Morningness-Eveningness Questionnaire (MEQ) became the most popular tool in evaluating daily preference of activity and sleep timing (Horne & Ostberg, 1976). MEQ is considered a self-report of how a person would prefer their daily sleep-wake rhythms to be timed, whereas chronotype is thought to represent a circadian trait; phase of entrainment, or internal time (Roenneberg, 2015).

All parameters listed above depend on several factors. Sleep duration and need for sleep have a moderate genetic component, with some reports suggesting a heritability of 30-44 % (Goel, 2017; Ollila et al., 2014; Tafti, Maret, & Dauvilliers, 2005; Touchette et al., 2013). A genetic predisposition for short sleep may result in sleep duration as short as 6 hours being sufficient (He et al., 2009). This is, however, extremely rare; although up to 11.8 % of 444306 American adults report sleeping 5 hours or less, the reason for this may be insufficient sleep or insomnia rather than actual short sleep need (Liu et al., 2016). The prevalence of long sleep duration extending over 10 hours in adulthood is less than 4 %.

Genetics have an even more influential role in circadian regulation (estimates of heritability up to 50 %)(Franken & Dijk, 2009), and the interaction between process C and S (Dijk & Archer, 2010). The genetic background for dyssomnias and parasomnias is estimated to explain a varying amount of the phenomena, with some dyssomnias such as narcolepsy having a heritability of 25-31 % while parasomnias and other complex disorders seem more dependent on environmental triggers (Tafti et al., 2005).

In addition to genetic influences, sleep behaviour is also controlled by habitual and environmental cues, such as zeitgebers. Zeitgebers pace the circadian clocks which result in Process C; they act as external cues that entrain an organism's biological rhythms according to the environment

(Roenneberg & Merrow, 2007). Based on both internal and external factors, a person's circadian rhythm sets a pace for when to engage in daily activities, and when to rest, and it is associated with health outcomes, behaviour, and performance. Optimal timing of diverse biochemical processes is likely to result in efficient and well-toned cellular functioning. When a person's circadian clock is synchronized with the environment, performance is more likely to reach full potential. This operating efficiency is likely to influence both physiological markers such as metabolism involving lipids and hormones (discussed in 2.3) and cognitive phenomena (discussed in 2.2).

2.1.3.1 Across the universe

During the past 100 years, anecdotal evidence suggests the amount of sleep has diminished. Based on published research, the decrease is about 70 minutes over the past 100 years (Matricciani, Olds, Blunden, Rigney, & Williams, 2012). This has been attributed to the growing amount of electric light, tightly scheduled hectic lifestyles, or, simply differences in measurement. The amount of sleep in contemporary hunter-gatherer groups was recently studied in order to resolve whether there is a difference between human ancestors' sleep duration and the current sleep behaviour (Yetish et al., 2015). The study reported a mean duration of six-and-a-half hours among three different tribes, suggesting no diminish in sleep duration over the course of recent advances in technology.

Due to lifestyle and cultural differences, as well as possible ethnicity-related genetic influences, there are, however, some regional differences in sleep behaviour. Within a sample of 2590 preschool children from all over the world, differences are already present: bedtimes may vary from 7:30 pm to 10:30 pm, and mean total night time sleep durations varied from less than 9 hours to almost 11 hours (Mindell, Sadeh, Kwon, & Goh, 2013). Adolescence introduces one source of variation: in western cultures, teenage years bring along the emergency of striving for autonomy and social pressure for late-night activities, whereas in more economically challenged settings a teenager may already be in full-time employment with little free time (Walch, Cochran, & Forger, 2016).

The prevalence of morningness is more common in people with specific ethnic backgrounds such as African English (Malone, Patterson, Lozano, & Hanlon, 2017). A recent review found that racial or ethnic differences account for some of the variation in sleep duration in America, with a higher prevalence of both short (≤6 hours) and long sleep (≥9 hours) among those with black ethnicity (Adenekan et al., 2013). One study reporting ethnic or racial reasons for sleep disturbances found a higher prevalence of short sleep in Black, Hispanic, and Chinese people

than in white ethnicity (Chen et al., 2015). Similarly, they reported higher prevalence of sleep disordered breathing in people from both Hispanic and Chinese descent. These differences highlight the genetic and cultural aspects of sleep behaviour.

2.1.3.2 Across the ages

New-born infants sleep as much as 22 hours per 24 hours (Iglowstein, Jenni, Molinari, & Largo, 2003). Gradually, time spent awake tends to increase alongside neural maturation and, finally, degeneration: sleep duration reports in elderly people suggest a typical 6 to 8 hours of sleep per 24 hours (Van Den Berg et al., 2008). Sleep duration, quality, timing, and architecture change over typical development, though not in a linear fashion (Barclay & Gregory, 2014; Ohayon, Carskadon, Guilleminault, & Vitiello, 2004). Table 1 summarizes the parent- or self-reported mean levels of sleep duration over development from infancy to adolescence (Iglowstein et al., 2003). Typically the number of reported sleeping hours depends heavily on the measurement method: self-reported measures over-estimate the duration when compared to actigraphy or PSG. Actigraphy may under- or over-estimate the amount of sleep depending on the sensitivity settings of the device (Girschik, Fritschi, Heyworth, & Waters, 2012; Meltzer, Montgomery-Downs, Insana, & Walsh, 2012). When comparing measures, the selected method should always be taken into consideration.

Table 1. Mean parent- or self-reported sleep duration from infancy to adolescence (Iglowstein et al. 2003)

	Age in years										
	1	3	5	7	9	10	12	13	14	15	16
Total sleep duration (h)	13.9	12.5	11.4	10.6	10.1	9.9	9.3	9.0	8.7	8.4	8.1
SD	1.2	1.1	0.9	0.7	0.6	0.6	0.6	0.7	0.7	0.7	0.7

We have recently reported sleep duration derived from actigraphy measurements, and showed that in Finnish 8-year-olds, the mean of both week and weekend sleep duration was 8.5 and 8.2 hours for girls and boys, respectively. At 12 years of age, both boys and girls slept a mean of 7.8 hours on weekdays, whereas the duration of weekend sleep was 8.5 hours for girls and 8.3 hours for boys (Pesonen et al., 2014). This suggests a profound change in sleep duration during the transition from childhood to adolescence. These changes include delayed sleep phase (M. A. Carskadon, Vieira, & Acebo, 1993) as well as changes in sleep architecture (Tarokh, Van Reen, LeBourgeois, Seifer, & Carskadon, 2011). It is likely that these changes

in sleep reflect cortical restructuring such as synaptic pruning, which is ongoing from early adolescence until young adulthood (Tarokh et al., 2011). Some studies suggest that physical pubertal changes emerge later than those seen in sleep (Sadeh, Dahl, Shahar, & Rosenblat-Stein, 2009), implying that physical, secondary pubertal changes emerge after children's sleep is already developing into adolescent sleep.

Mean-level variation between children's and adolescents' sleep is due to developmental occurrences in neural systems, such as the myelinated nerve fibres in the limbic system and amygdala as well as growth of white matter in the developing brain during adolescence (Paus, 2010; Vink, Derks, Hoogendam, Hillegers, & Kahn, 2014). This is thought to be partially generated by testosterone-driven changes, explaining some of the sexual dimorphisms in adolescence (Paus et al., 2010). Neural development may be reciprocally associated with sleep need and duration, with sleep deprivation causing some changes and morphological differences being the source of some sleep features (Ma, Dinges, Basner, & Rao, 2015).

Inter-individual differences in sleep changes are mostly dependent on genetic differences, environmental factors (Sletten et al., 2013), and an interplay of these (Tafti et al., 2005). Adolescence is considered a sensitive period in sleep, as it is typically one of the most vulnerable times regarding psychiatric, psychological and social problems which are closely associated with sleep behaviour (Barclay & Gregory, 2014; Paus, Keshavan, & Giedd, 2008). There are several factors which delay the adolescent sleep timing and circadian rhythm (M. A. Carskadon, Wolfson, Acebo, Tzischinsky, & Seifer, 1998). The diminishing influence of parents on bedtimes, increased influence of time spent consuming various media contents, time-consuming activities such as hobbies and first experiences of employment, and the desire for greater independence may all influence sleep timing. Intrinsic regulatory mechanisms in adolescents include an ability to resist sleep pressure, and a later onset of melatonin, resulting in a later circadian preference. As these mechanisms accumulate, they may exponentially delay the signal for melatonin production (M. A. Carskadon, Acebo, & Jenni, 2004).

Adolescents also have a relatively high prevalence of circadian regulation problems, insomnia, and daytime sleepiness (Gradisar et al., 2011). Additionally, homeostatic sleep pressure builds up differently as more mature adolescents accumulate sleep pressure at a slower rate. Later sleep timing and weekend catch-up sleep further delay the signal for melatonin production, which then accumulates into higher prevalence of circadian regulation problems, and overall delayed sleep phase. (M. A. Carskadon, 2011)

2.2 COGNITIVE PERFORMANCE AND SLEEP

Cognitive abilities and functions can be considered either trait- or state-like features. Intelligence is thought to be a relatively stable ability ('trait'), with little variation depending on circumstances, whereas some subtypes of memory and executive functions (EFs) may be more dependent on the person's state (Friedman et al., 2016). The correlation between trait- and state-like features in human cognition understandably varies greatly over reported studies, but trait-like cognitive abilities are thought to explain some variation in state-dependent task performance. One study reported a correlation of 0.31 between IQ and the inhibiting and shifting factors of executive functioning, and a significant correlation of 0.68 between IQ and the updating factor of EF, suggesting partial overlap for IQ and some EFs (Friedman et al., 2006).

The relationship between sleep and cognitive functioning is a complex one, with most studies suggesting minor associations between sleep and the more stable, trait-like abilities such as intelligence (Astill, Van der Heijden, Van Ijzendoorn, & Van Someren, 2012). As well as being minor, the reported associations have variance in direction: some studies suggest a negative association with intelligence and habitual sleep duration (Gruber et al., 2010) whereas a few studies have reported a positive association and report that shorter sleep duration or poorer sleep quality may be associated with better cognitive abilities (Geiger, Achermann, & Jenni, 2010a). The reason for this heterogeneousness is likely to be caused by methods and at least partially explained by participant selection.

The methods used in measuring cognitive performance are, in most reported studies, validated tests. While these tests are accurate measures of cognition, they do not measure other aspects of a person, which may interfere with the association between sleep and cognition. For instance, the onset of pubertal development is an aspect which influences both cognitive test outcomes and sleep behaviour in children and adolescence. Other relevant aspects might be partially innate (i.e. the genetically determined need for sleep, or, certain polymorphisms in the gene PER3, conferring cognitive susceptibility to total sleep deprivation (Groeger et al., 2008)), or, acquired, such as improved performance as a result of training. Additionally, environmental and genetic influences may interact in a way that is not yet known. Thus, several confounders or covariates need to be considered in determining the associations between sleep and cognitive abilities.

One recent meta-analysis demonstrates the detrimental effect of insufficient sleep on state-dependent cognitive performance (Lowe, Safati, & Hall, 2017). The value of "optimal sleep" seems to be well recognized in both clinical and scientific fields, though optimal sleep is difficult to define: there

is great individual variation in biological sleep need, and sleep behaviour may vary according to several external factors as discussed above. Lack of daytime sleepiness is a good indicator of sufficient sleep, but this, too, is subject to exceptions. Disorders such as irregular sleep-wake rhythm, or any illnesses which include daytime fatigue may convey an impression of insufficient sleep though this is not always the case. Similarly, shift workers may experience daytime sleepiness due to sleep rhythm variation even though their sleep duration per se would be sufficient (Vetter, Juda, & Roenneberg, 2012). Hence, optimal sleep needs to be defined individually, and as an intertwined occurrence of sufficient sleep duration which occurs under appropriate circumstances (i.e. the right time, the right place).

One recent study (Kocevska et al., 2017) reported that sleep duration has a non-linear association with childhood cognitive measures in Dutch 6-year-olds, with both longer and shorter sleep duration being associated with poorer performance in validated measures of cognitive development (both nonverbal and language development). Additionally, frequent awakenings were associated with lower nonverbal intelligence (Kocevska et al., 2017). A recent sleep restriction study (Ong, Lo, Gooley, & Chee, 2016) investigated thoroughly the long-lasting effects of insufficient sleep on sleep architecture in 15 to 19-year-olds: even after 5 nights of non-restricted sleep, the significant differences in adolescent sleep architecture were still present between those with restricted sleep, and those with no restriction. The effects of shorter sleep on cognitive performance and daytime functioning may be due to sleep architectural alterations, although other hypotheses have also been suggested (Vriend, Davidson, Rusak, & Corkum, 2015).

Recent studies have recognized the significant effect of circadian misalignment in explaining differences in cognitive test scores (Paech, Crowley, & Eastman, 2017). Sleep timing and circadian phase are likely to influence the ability to consolidate various types of material into memories, thus enabling learning; this has been demonstrated by experimental studies in laboratory settings, as well as learning effects in shift-workers (Krishnan & Lyons, 2015). These studies suggest an effect of circadian misalignment in at least some cognitive domains. The domain-specific findings related to sleep are described in more detail in the following paragraphs.

2.2.1 EXECUTIVE FUNCTIONS AND MEMORY

Both executive functions and memory are hypernyms, which embed several subdomains (Jurado & Rosselli, 2007), some which are inter-related. Dividing EFs and different types of memory processes may be an artificial division; most processes require both memory and some executive control in

order to be successfully completed. Although the following paragraphs discuss distinct features of EF domains and specific memory categories, the division between these fields of cognition is not categorical.

Several sleep deprivation studies have shown a causal relationship between insufficient sleep duration and poor executive function (Killgore, 2010; Lo et al., 2012; Rossa, Smith, Allan, & Sullivan, 2014; Slama et al., 2017; Tucker, Whitney, Belenky, Hinson, & Van Dongen, 2010; Vartanian et al., 2014; Whitney & Hinson, 2010), as well as weaker performance in tasks demanding memory capacity (Kopasz et al., 2010). To what extinct this deterioration is a result of sleep deprivation in one specific domain is still under debate, as it is evident that tasks measuring EFs are likely to additionally tap into other abilities (Rana et al., 2017).

A similar problem in detecting the genuine effects of poor sleep is the comorbidity problem in studies investigating sleep-related effects on cognitive performance in individuals suffering from neuro-developmental disorders such as depression, ADHD, or anxiety (Gruber et al., 2011; Moreau, Rouleau, & Morin, 2013). Epidemiological studies investigating the associations between naturally occurring sleep and cognitive performance during typical development are sparse.

The estimated effect of sleep restriction has been demonstrated by one study which suggested that sleep deprivation causes a dose-response effect on cognitive performance in young, healthy adults (Rossa et al., 2014): the more sleep deprived a person is, the weaker their inhibitory control and attention levels are likely to be. Adolescence is a time period with dynamic neural development and social pressure for risk behaviour, and sleep restriction is likely to have an even more profound effect on executive functions and inhibitions in adolescence.

The specific associations between different executive functions and sleep are discussed in the following paragraphs.

2.2.1.1 Self-regulation, attention, and sleep

Self-regulation is understood to be a multi-dimensional ability which affects the flexible regulation of cognition, behaviour and emotions. This ability is manifested in everyday life as well as under controlled laboratory conditions. Self-regulatory skills are partly trait-like, stable features of a person's behaviour, but also fluctuating states which may be altered for instance during illness, fatigue, stressful conditions, hunger and other physiological states. Trait-like EFs may be evaluated using questionnaires or self-reports, whereas state-like EFs may be measured using tests of performance.

Self-regulation is governed by various brain regions such as the prefrontal cortex and the amygdala which undergo profound developmental

changes during adolescence (Casey, 2015). The function of these regions is adversely affected by insufficient sleep, thus, sleep may play a key role in maintaining optimal executive functioning during adolescence (Telzer, Fuligni, Lieberman, & Galvan, 2013; Telzer, Goldenberg, Fuligni, Lieberman, & Galvan, 2015).

Experimental sleep studies have demonstrated mixed effects of sleep deprivation on self-regulatory abilities, although all studies suggest some deterioration in performance following sleep restriction. Partial sleep deprivation, such as restricting time in bed to 6.5 hours compared to 10 hours, resulted in inattentive behaviour and sleepiness in one recent study (Beebe, Field, Milller, Miller, & LeBlond, 2017). Total sleep deprivation of one night is reported to lead to slower reaction times, weaker sustained attention, and increased cognitive processing speed in adolescents aged 14 to 18 years (Louca & Short, 2014).

A recent study in young adults demonstrated the differentiated effects of experimental sleep deprivation on attentional failures or lapses in task-goal switching (Slama et al., 2017). Task-goal switching is a common method used in experimental studies: the participant is required to alternate between two or more tasks (Kiesel et al., 2010). Switching leads to more errors and slower performance than completing the tasks individually without switching. In their study, the authors reported poorer attentional and inhibition measures in the sleep deprived participants, but no significant effect on working memory.

While both divided and sustained attention seem to be weaker after sleep deprivation, some studies have also reported null-findings in adults (Cain, Silva, Chang, Ronda, & Duffy, 2011; Tucker et al., 2010). These null-findings are likely to be caused by practice effect, as some of the participants went through up to 13 Stroop tests prior to beginning the sleep loss portion of the study, and, possibly, due to circadian phase. One study reported the associations between sleep duration, circadian phase, and different cognitive domains including alertness, sustained attention, working memory/executive functions, motor control, and, temporal control, and concluded that deterioration in performance is domain-specific, and depends on prior accumulated sleep debt, circadian phase at which performance is assessed, and, on the subject's genetic features (Lo et al., 2012). These are typically not controlled for in all studies, which limits the generalization of the findings.

Another study examining the associations between different cognitive domains and both sleep duration and circadian phase in adults (n=6, mean age 27 years). They reported different areas of vulnerability, but in their study, the strongest association was found between circadian phase and inhibitory control, while the drowsiness present immediately after awakening (sleep inertia) modulated selective visual attention for a spatial-configuration search task (Burke, Scheer, Ronda, Czeisler, & Wright, 2015).

Several studies report findings from artificially induced sleep restriction settings. Based on a recent review, sleep restriction seems to selectively impair sustained attention, executive function, and long-term memory (Lowe et al., 2017). It seems evident that sleep restriction impacts cognition negatively, but less is known about the effects (or associations) of normal variation on daytime functioning. Habitual sleep behaviour may have different causes and consequences as compared to experimentally altered sleep.

One study in typically developing adolescents using self-reported sleep measures reported weaker self-reported executive functioning among those with high levels of daytime sleepiness and later chronotype (Owens, Dearth-Wesley, Lewin, Gioia, & Whitaker, 2016). In that study, sleep timing and daytime sleepiness were more powerful predictors of poor executive function than short sleep duration. In another study Warren et al. concluded that sleep duration, but also earlier weekend bedtimes may improve executive functioning and furthermore be reciprocally related to self-regulation. They report findings from 709 schoolchildren (Warren, Riggs, & Pentz, 2016).

Another study (Wilckens, Woo, Kirk, Erickson, & Wheeler, 2014) using objective measures reported that poorer sleep quality had an association with weaker executive functioning in both older (n=53, mean age 63 years) and younger (n=59, mean age 23 years) adults, but that only younger adults' sleep quantity was associated with poorer working memory performance and verbal fluency. This suggests that naturally occurring sleep duration may be more important for cognition in young adults than in older individuals.

Based on the studies mentioned above, it seems likely that habitual sleep duration, quality, and timing have differentiated associations on executive functioning, and that these associations may also differ according to age.

2.2.1.2 Memory and sleep

Memory is a central provider for efficient cognitive processing. It can be divided into at least three subtypes: sensory memory, working memory, and long-term memory. Long-term memory can be further divided into procedural memory and declarative memory, and sometimes other categorizations are also presented. The division between different domains of cognition is not clear-cut: working memory may be perceived as a part of executive functioning instead of a specific memory sub-domain. Additionally, definitions often depend on the research field, i.e. neuroscience may divide memory types based on the brain region which is activated during a certain

type of memory task. Different types of memory are likely to correlate with intelligence to some extent, with estimates in working memory ranging from approximately 0.60 to 0.70 (Conway, Kane, & Engle, 2003) which further complicates the investigation of domain-specific associations.

Memory performance is heavily dependent on sleep (Diekelmann & Born, 2010). During sleep, physical processes enable pruning and strengthening of material that is either remembered or forgotten, based on e.g. what material has emotional content, other relevance, or, requires further processing (Diekelmann et al., 2009). Similarly, sleep supports forgetting unnecessary information. The process of reorganizing and consolidating memories is thought to be one of the central functions of sleep (Landmann et al., 2014).

The neural mechanisms behind the sleep-dependent memory process have been preliminarily described and hypothesized in several reports (Landmann et al., 2014), with one significant element assumed to be spindle activity (Fogel & Smith, 2011; Hennies, Lambon Ralph, Kempkes, Cousins, & Lewis, 2016). Sleep spindles are bursts of neural activity as measured by thalamo-cortical oscillations in the 10-16 Hz range, typically during N2 (De Gennaro & Ferrara, 2003). As the brain processes material during sleep, it both prunes and strengthens synaptic associations, or memories, according to what is relevant (Cherdieu, Versace, Rey, Vallet, & Mazza, 2017). One of the proposed mechanisms involves transforming primary synaptic plasticity processes into more permanent forms by promoting structural plasticity (Ulrich, 2016).

The consolidation of declarative, procedural and emotional memories is known to depend on post-learning sleep (Landmann et al., 2014; Prehn-Kristensen et al., 2013; Schonauer, Pawlizki, Kock, & Gais, 2014). Different types of memory performance may be dependent on different aspects of sleep: already rather short sleep periods, such as 1-2 hours, may be beneficial for declarative memory consolidation, whereas procedural memory benefits from post-learning sleep in a dose-response manner (Diekelmann et al., 2009). The close relationship between executive function and working memory suggests that working memory may be similarly dependent on sufficient sleep duration as executive functioning. This may be due to the cyclic nature of overnight sleep stages: insufficient sleep duration leads to less opportunities for stage-dependent memory consolidation.

A review on the associations between memory and sleep in healthy children and adolescents concluded that performance in complex tasks is more likely to be impaired after sleep restriction than in simple memory tasks (Kopasz et al., 2010). Based on 15 studies in children and adolescents the authors suggest that sleep promotes memory encoding, working memory and memory consolidation in children and adolescents. However, different memory systems should be investigated separately in children; implicit memories seem to lack sleep-related consolidation in childhood (Kopasz et al., 2010). Understanding the cognitive factors that contribute to the

associations between sleep and memory performance is still incomplete – one explaining factor may be general intelligence (Fenn & Hambrick, 2015).

2.2.2 INTELLIGENCE AND SLEEP

A recent study in a large cohort of adults (n= 477529, mean age 57 years) suggested only little associations between sleep and intelligence, evaluated as test performance in reasoning, basic reaction time, numeric memory, visual memory, and prospective memory (Kyle et al., 2017). During earlier development, the associations may be difficult to evaluate, as they may be influenced by neural development per se, and several state-dependent factors. Studies in children have reported mixed results, which may be due to different measurement methods, not taking into account several confounding issues, and, using heterogeneous samples with large age ranges. Some studies use parent-reported sleep measures while others measure sleep objectively. Various measures of cognitive performance have been reported, with some studies investigating the associations between sleep and intelligence test performance whereas others report academic performance (Astill et al., 2012).

Some studies reported objective measures of sleep and an association between longer sleep and higher intelligence levels (Gruber et al., 2010; Paavonen et al., 2010), but one has suggested a opposite association (Geiger et al., 2010a). Null findings are also commonly reported (Astill et al., 2012; Nixon et al., 2008). It is possible that these controversial results are due to non-linear associations between sleep and intelligence (Kocevska et al., 2017). Typically, both long and short sleep are associated with poorer outcomes; this has also been reported in older adults regarding cognition (Lo, Groeger, Cheng, Dijk, & Chee, 2016).

In addition to sleep duration, one recent study has investigated the influence of weekday bedtimes on cognitive performance in early childhood in a sample of n=11178 at ages 3, 5 and 7 years (Kelly, Kelly, & Sacker, 2013). Regular bedtimes during early childhood were related to better cognitive performance, even when controlled for socio-economic status.

A recent study in young adults (n=435, age 18-35 years) investigated the effect of general intelligence on sleep-dependent memory consolidation (Fenn & Hambrick, 2015). They estimated intelligence as performance in working memory capacity, fluid intelligence, crystallized intelligence, and verbal fluency, and found that those with higher general intelligence showed greater memory gain and less loss during sleep.

2.3 HEALTH AND SLEEP

Sleep quantity, quality, schedules and architecture have genetic, environmental, and habitual grounds. These may be related to several health-related aspects, and may not necessarily be independent predictors of sleep behaviour. Recent meta-analyses report elevated health risks relating to both short and long sleep duration (Li et al., 2016; Lu et al., 2017; Wang et al., 2016; Yin et al., 2017).

2.3.1 METABOLISM

Short sleep duration and poor sleep quality are associated with obesity and elevated body mass index (BMI) in many epidemiological studies, as shown in recent meta-analyses in paediatric populations (Fatima, Doi, & Mamun, 2015, 2016). There are several pathways that could link insufficient sleep to obesity, weight gain, and other adverse metabolic outcomes. These pathways include increased food intake, decreased energy expenditure, and changes in levels of leptin and ghrelin, which regulate appetite. Additionally, lifestyle choices and social activities such as unhealthy dietary choices, binge-watching TV series, engaging in social media in the evening, may lead to sleep deprivation and further explain some of the association (Bayon et al., 2014).

Short sleep duration is known to cause inflammation (Kanagasabai & Ardern, 2015), which is also connected to the pathophysiology of various metabolic diseases' development. Sleep problems, such as insufficient sleep and circadian misalignment, may contribute to metabolic dysregulation (Depner, Stothard, & Wright, 2014). Insufficient sleep causes strain on the immune system and glucose metabolism – these associations have been established in many studies (Shan et al., 2015), while studies on lipid metabolism have been less frequent.

2.3.2 CARDIOVASCULAR RISKS

Kruisbrink et al. reported associations between blood lipids and sleep from adult samples in a review article (Kruisbrink et al., 2017), and found no significant relationship between sleep duration and the development of dyslipidaemia, but also remark that the studies included in the review had limitations and heterogeneity in methods. One study using objective

measurements of sleep in a community cohort of children aged 4-10 years (including overweight and obese children) reported that longer sleep duration and regular sleep patterns had a beneficial effect on lipid measures (Spruyt, Molfese, & Gozal, 2011). Shorter sleep duration and irregular sleep patterns were associated with higher levels of plasma fasting insulin, low-density lipoprotein cholesterol (LDL-C), and C-reactive protein concentrations. One study in obese 11- to 17-year-old adolescents found an association between short sleep duration and overall cardiometabolic risk score scores, derived from waist circumference, mean arterial pressure, fasting high-density lipoprotein cholesterol (HDL-C), triglycerides (TGs), and, glucose (Iglayreger et al., 2014). Two recent studies in children and adolescents have not found associations between objectively measured sleep and lipids (Kong et al., 2011; Sung et al., 2011). The studies are cross-sectional, which may limit the representativeness of the findings. One longitudinal study using self-reported sleep measures and self-reported responses to the question "Has a doctor ever told you that you have high cholesterol?" reported a robust finding in relation to shorter sleep as an elevated risk for hypercholesterolemia (Gangwisch et al., 2010). One longitudinal study in small children used annual self-reported sleep duration over 24 hours as a measure of sleep over seven years, and concluded that chronic insufficient sleep was associated with higher metabolic risk as measured by waist circumference, blood pressure, HDL-C, TGs, and insulin resistance (Cespedes et al., 2014). There is thought to be a common molecular basis for sleep duration and lipid metabolism (Ollila et al., 2012).

3 AIMS OF THE STUDY

Previous studies have strongly suggested that insufficient sleep may have detrimental effects on health and cognitive functioning. This has been studied mostly in singular cognitive domains, and cross-sectionally. Sleep deprivation studies have demonstrated the effects of insufficient sleep among adolescents and young adults, but translating the findings into the effects of naturally occurring sleep deprivation is still ongoing. The goals of this work were to investigate habitual sleep over development from childhood to young adulthood, and to study sleep-related aspects of cognitive performance and health. I hypothesized that sleep is associated with cognitive functioning in several domains, as well as with lipid profiles – specifically, that poorer sleep is associated with poorer cognitive functioning and lipid profiles. Additionally, I hypothesized that sleep timing and duration would differ between circadian preference groups during development.

The specific goals of this thesis were:

1. To study the cross-sectional associations between neurocognitive functioning and habitual sleep duration and sleep quality in early adolescence **(Study I)**

2. To study the longitudinal associations between naturally occurring sleep and lipid profile in early adolescence **(Study II)**

3. To study the sleep behaviour associated with young adults' executive functioning **(Study III)**

4. To study the developmental trajectories of sleep timing from middle childhood to adolescence from a circadian preference perspective **(Study IV)**

4 MATERIALS AND METHODS

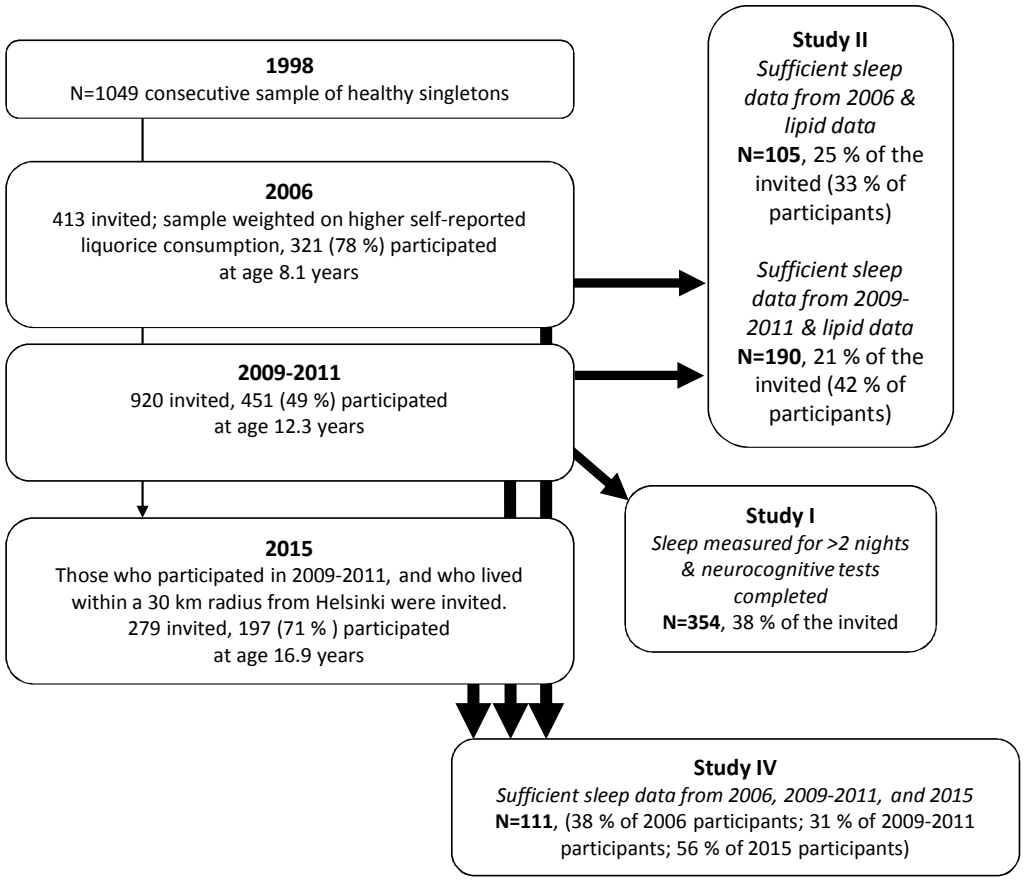
4.1 COHORTS

Studies I, II, and IV in children and adolescents were conducted within the same Glaku cohort, described below. The young adult participants for Study III were recruited from Arvo Ylppö Longitudinal Study (AYLS).

4.1.1 GLAKU

The participants for Studies I to III came from an urban community-based cohort comprising 1049 infants born between March and November 1998 in Helsinki, Finland (Strandberg, Jarvenpaa, Vanhanen, & McKeigue, 2001). The study design and selection of participants is presented in Figure 1. The initial research question in the Glaku cohort aimed at detecting the adverse effects of prenatal glycyrrhizin during development, namely in the form of maternal liquorice consumption. Glycyrrhizin is naturally present in liquorice, and acts as a potent inhibitor of placental 11β-hydroxysteroid dehydrogenase type 2, the barrier to maternal glucocorticoids. High liquorice consumption thus exposes the offspring to higher levels of glucocorticoids and potentially creates a stressful prenatal environment. We have reported findings from the adverse effects of high liquorice consumption on development (Raikkonen et al., 2017).

Figure 1. The Glaku study design and selection of the participants for studies I, II, and IV.



4.1.2 AYLS

The participants for Study III came from the Arvo Ylppö Longitudinal Study (AYLS), which is part of a multicentre follow-up study conducted in Uusimaa, Finland, and Bavaria, Germany (Heinonen et al., 2008; Wolke, Sohne, Riegel, Ohrt, & Osterlund, 1998). Participants were recruited from a total of 15311 deliveries in the seven maternity hospitals of Uusimaa province between March 15th, 1985 and March 14th, 1986.

The sample comprised 2193 infants. 1535 were admitted to the neonatal wards within obstetric units or transferred to the Neonatal Intensive Care Unit of the Children's Hospital within ten days of birth. An additional 658 who had not been admitted to neonatal wards were prospectively recruited from births after every second hospitalized infant from three of the largest maternity hospitals of Uusimaa. Of the 2193 infants, 1913 subjects could be traced as adults and were invited to participate in a follow-up study during the years 2009–2011. Of the invited, 991 subjects, (52% of the invited; 48% men), participated in a clinical study at Folkhälsan Research Center, Helsinki, Finland. Of them, 805 were born full-term (gestation age ≥37 weeks), which was the inclusion criteria for study III.

4.2 MEASURING AND EVALUATING SLEEP

Sleep quantity is the most commonly measured features of sleep; it can be estimated relatively easily by asking a person, or by observing their behaviour. The most commonly used measures of sleep are self-reports, or in the case of paediatric sleep research, parental reports. The problems relating to self- or parent-reported sleep have been documented: parents cannot reliably estimate the sleeping schedules of their children even as young infants (Werner, Molinari, Guyer, & Jenni, 2008). Similarly, self-reports of sleep tend to overestimate the amount of true sleep, although over a long period of time self-reports may be sufficiently accurate in reporting habitual sleep duration (Girschik et al., 2012). PSG is the golden standard in measuring true sleep, but PSG measurements are far too strenuous to be used as a tool in epidemiological studies, or in long-term measurements of typical sleep behaviour. For the purposes of epidemiological studies, an affordable and easily administered option for objective measurements of sleep is wrist-worn accelerometers (actigraphy). All the studies in this thesis build on the use of actigraphy, which is described in detail below.

4.2.1 ACTIGRAPHY

Accelerometers are widely used in measuring movement, and the resulting information can be utilized in order to estimate various aspects of movement, or, in the case of sleep, non-movement. Actigraphy is a widely used objective method which has been used to study sleep–wake patterns for over 45 years (Kupfer, Detre, Foster, Tucker, & Delgado, 1972). In sleep research, accelerometers are typically embedded in actigraphs, wrist-worn devices which calculate movements of the hand during sleep time. Actigraphy-derived estimates of sleep are based solely on movement, so they do not detect sleep stages or events such as parasomnias.

While PSG is considered the most reliable and detailed measuring method in sleep medicine, epoch-by-epoch comparisons of PSG and actigraphy yield sensitivity up to 0.97, specificity up to 0.77, and, accuracy up to 0.90 in detecting sleep from wake (Meltzer, Walsh, Traylor, & Westin, 2012). While accuracy and sensitivity for detecting sleep are typically high when comparing actigraphy to PSG, some studies have reported weak specificity in detecting wake (Sadeh, 2011).

In studies I-IV sleep was objectively measured using omnidirectional accelerometers using piezoelectric technology. In study I and IV, we used Actiwatch 7 (AW7, Cambridge Neurotechnology Ltd., UK), while in studies II and IV, longitudinal data collection was done using both Actiwatch AW4 and AW7. The technology is essentially the same in AW4 and AW7 devices, although some differences exist: the AW7 is lighter, and has longer battery life, but both measure acceleration similarly.

Figure 2. A representation of the piezoelectric technology in accelerometers. The seismic mass squeezes the piezoelectric material, which generates a voltage. Modified from *Measuring Vibration with Accelerometers - National Instruments* http://www.ni.com/white-paper/3807/en/

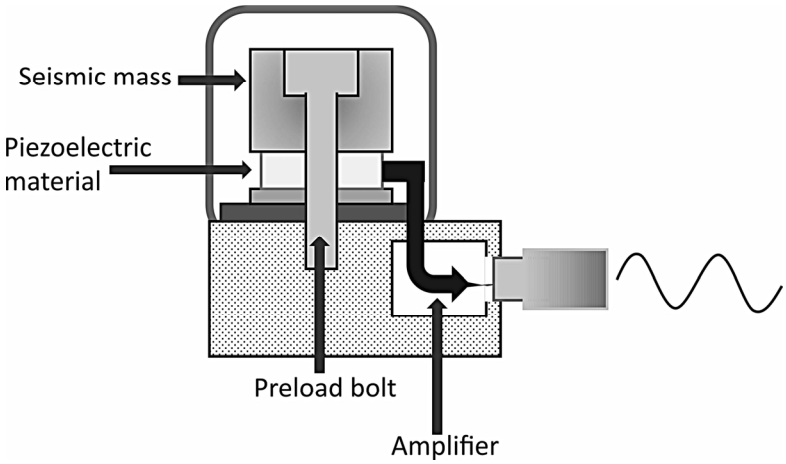


Figure 3. The Actiwatch 7. During the day, it measures physical activity, and in nighttime measures, it is a tool for estimating sleep from wake.

The data handling procedure was similar in all studies. The Actiwatch was worn on the non-dominant wrist (see Figure 3.). The participant or their caregivers were instructed to keep a sleep diary on bed times ('lights off') and get-up times and to press a button/event marker on the device at those times. The data were visually inspected for any discrepancies between the sleep diary, event markers, and physical activity data.

The following events led to the exclusion of that specific night from the data: the device was not used, no information on bedtimes was given, the participant was already sleeping at reported bedtime according to the data, information on wake up time was not given and was not interpretable from the physical activity data, or there were changes to normal routines due to, for example, illness or travel.

Data were scored using Actiwatch Activity & Sleep Analysis software (versions 5.42 and 7.0) with medium sensitivity and 1-minute epochs. We used the validated Actiwatch algorithm (Meltzer, Montgomery-Downs, et al., 2012).

4.2.2 SLEEP VARIABLES

In studies I-IV we used actual sleep duration as a measure of sleep duration – this is determined by the actigraph's algorithm and excludes epochs considered as wake. Sleep quality was defined as sleep efficiency (percentage of time in bed spent asleep), WASO, or fragmentation index. Additionally, two sleep regularity variables were calculated. Weekend catch-up sleep, which is calculated as the difference between weekend and weekday

sleep duration. In study III we also calculated a coefficient of variation (standard deviation of sleep duration divided by individual average of sleep duration x 100) to operationalize sleep duration irregularity (Rowe et al., 2008).

For studies III and IV circadian rhythm was defined as sleep midpoint over both weekday and weekend nights. Midpoint was calculated as the time when half of the assumed sleep duration had passed since sleep onset.

4.2.3 CIRCADIAN PREFERENCE

For study IV we calculated a morningness-eveningness score using a questionnaire. The original MEQ (Horne & Ostberg, 1976) consists of 19 questions, including items such as "How alert do you feel during the first half hour after you wake up in the morning?", and "If you had no commitments the next day, what time would you go to bed compared to your usual bedtime". The MEQ results in a continuous score, with those scoring higher having higher levels of morningness. We estimated circadian preference using a shortened version of MEQ (Hatonen, Forsblom, Kieseppa, Lonnqvist, & Partonen, 2008). Based on a 6-item reduced version (rMEQ, using questions 4, 5, 15, 16, 17, and, 19), we calculated a continuous score and used cut-off points 5-12 for eveningness, 13-18 for intermediate, and 19-27 for morningness.

4.3 MEASURING COGNITIVE OUTCOMES

4.3.1 EXECUTIVE FUNCTION

In studies I and III, performance-based EF was evaluated using the Trail Making Test (TMT) consisting of two parts, and a computerized versions of Conners' Continuous Performance Test II (CPT).

The TMT (Reitan, 1958) consists of parts A and B, which require simple motor skills and attention. Part B depends additionally on executive control, mental flexibility, divided attention and fluid intelligence (Salthouse, 2011). Lower scores indicate better performance. A proportional ratio score was calculated (B-A/A) in order to evaluate performance irrespective of motor skills. A smaller ratio score indicates a smaller difference between motoric performance and more complex processing.

The CPT (Conners, 2004) is a computerized test which measures sustained attention and inhibitory control in a task of responding to only target letters, resulting in hit reaction time, omission (failing to respond to a target) commission errors (false responses) and a D prime score estimating attentiveness.

Additionally, in Study I, the participants completed the Wisconsin Card Sorting Task (WCST)(Grant & Berg, 1948). In the WCST the participants are presented with one reference card and three to four choice cards. Every choice card matches a different feature of the reference card, and in every trial a feature is set as the rule which matches the reference to a choice. The rule may change as trials go on further, requiring the participant to change their response style. The WCST is thought to measure set-shifting, inhibition, set-maintenance, and rule detection (Jurado & Rosselli, 2007).

Additionally, in Study III, The Stroop test (Bohnen, Jolles, & Twijnstra, 1992) was administered. Stroop consists of Parts 1 and 2, and performance requires inhibition and selective attention: completing the task requires the participant to ignore the cue of the written word, and only say out loud the actual colour. An interference score (Part 2–Part 1) was calculated as a further measure of EF, with higher scores indicating poorer performance.

In study III, EF was evaluated using both self-reported and the performance-based measures described above. We used a validated 75-item adult version of the Behavior Rating Inventory of Executive Function (BRIEF-A) questionnaire (Roth, Isquith, & Gioia, 2005), which results in a Global Executive Composite (GEC) score. This can be broken down into two further indices: the Behavioral Regulation Index (BRI) and the Metacognition Index (MI). BRI evaluates the ability to control emotional responses and behaviour whereas MI evaluates the ability to solve problems via planning and organization, initiate tasks and activities, and organize the everyday environment. Higher scores indicate worse EF.

4.3.2 MEMORY

For study I memory was assessed with one subtest (Narrative Memory) from the Developmental Neuropsychological Assessment for Children II (Nepsy-II)(Korkman, Kirk, & Kemp, 2008), which requires the child to repeat an unfamiliar story as accurately as possible, and then to answer questions based on a story they heard.

4.3.3 INTELLIGENCE

For study I we used four subtests of the Wechsler Intelligence Scale for Children III (Wechsler, 1991) to assess verbal and perceptual reasoning: Vocabulary, Similarities, Picture Arrangement, and Block Design. Estimated Verbal IQ was calculated using standardized means from Vocabulary and Similarities, and estimated Perceptual IQ by using standardized means from Picture Arrangement and Block Design. Their composite score represents an estimate of the general IQ (Kaufman, Kaufman, Balgopal, & McLean, 1996).

4.4 MEASURING LIPID OUTCOMES

Following an overnight fast, blood samples were collected at a clinical visit between 8 a.m. and 10 a.m. Serum total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TGs) were analysed in the clinical laboratory of Helsinki University Hospital.

4.5 CENTRAL COVARIATES IN SLEEP STUDIES

For studies I, II, and IV we controlled for pubertal development using the Pubertal Development Scale (PDS). The PDS is a validated scale of pubertal maturation. For girls, the self-reported scale had 5-items: body hair, growth spurt, skin changes, menarche, and, breast development. For boys, the 3 first items were similar, but questions regarding facial hair and voice change were additionally rated. All the items were scored on a scale of no changes yet (1) to clear changes (3). In studies I and II we omitted the fourth option (development is complete) in all other scales except menarche (scored as 1 = no, 4 = has occurred) because of the young age distribution of our sample. In study IV, we used the full scale.

For study II, we used physical activity as one covariate. It was measured using the same accelerometers (Actiwatch AW7) and by calculating the daily activity count mean based on 1-minute intervals. The watch was worn on the non-dominant wrist for a minimum of 4 days at 12 years of age and data were analysed as described in detail previously (Martikainen et al., 2014).

For studies I and II, socioeconomic status was measured when the child was 12 years of age and defined as highest achieved education of either parent. Education was classified as secondary or lower, lower level tertiary, or upper level tertiary. For study III, socioeconomic status was defined as self-reported highest completed or soon to be completed education (from I = lower secondary to IV = university education).

For study I, maternal liquorice consumption was used as a covariate. It was classified as low (≤249 mg/week), moderate (250–499 mg/week), or, high (≥500 mg/week).

In studies I-III covariates included BMI (kg/m2), which was calculated based on weight and height measurements taken during a clinical visit.

4.6 STATISTICAL ANALYSES

IBM SPSS Statistics (versions 22.0-24.0) (IBM Corp., Armonk, NY, USA) was used for all statistical analyses and the significance threshold was set at .05.

For study I all the cognitive test scores were standardized for girls and boys separately, and age-residualized, and then transformed into T-scores (mean=50, SD=10). We used multiple linear regressions to study the continuous associations, and report unstandardized regression coefficients and 95% confidence intervals (95% CI). All statistical models in study I were adjusted for age, BMI, PDS score, SES, and, maternal liquorice consumption during pregnancy. One male participant needed to be excluded from sleep duration analyses due to an average sleep duration of over 5 standard deviations above mean.

For study II we standardized measures of sleep duration, WASO, and, weekend catch-up sleep at ages 8 and 12 years of age, and calculated the arithmetic difference, or, change, between these variables over 4 years.

We transformed all the lipid variables (HDL-C, LDL-C, TC, TGs) logarithmically to attain normality, and then standardized (mean=0, SD=1) them. We used multiple linear regressions to study the continuous associations, and report unstandardized regression coefficients and 95% confidence intervals (95% CI). We ran the analyses separately in girls and boys, as there were mean-level differences between girls and boys in both sleep and lipid measures. We estimated the associations between sleep and lipids using two different models: Model 1 adjusted only for age, and, Model 2 for age, BMI, PDS score, physical activity, and SES.

For study III we performed logarithmic transformations on all TMT indices, the Commissions score (CPT), and all BRIEF-A raw scores to normalize skewed distributions. To facilitate interpretation, all EF score variables were then transformed into T-scores. We used multiple linear regressions to study the continuous associations and used two different models: Model 1 adjusted for sex and age, and, Model 2, additionally for BMI and SES. To illustrate more clearly the associations between sleep and EFs we divided the sleep variables into thirds (or, tertiles) separately for men and women, and used analysis of covariance (ANCOVA) to compare mean differences (MDs).

For study IV we used a linear mixed model approach. First, we examined whether the overall level of sleep pattern across time differed between circadian preference groups (morning, intermediate, and, evening types), and then whether the sleep pattern trajectory developed differently across the time points depending on the circadian preference. Finally, as post-hoc analyses we used ANCOVAs for the statistically significant outputs from the mixed models to calculate the MDs between all three different circadian

preference types. We adjusted for age at the time of sleep measurements and sex.

4.7 ETHICS

The Ethical Committee of the City of Helsinki Health Department and the Ethical Committee of the Helsinki University Hospital for Children and Adolescents at Helsinki and the Uusimaa Hospital District approved the Glaku studies (I, II, IV). Regarding Studies I and II, parents and children gave informed, written consent or assent, and regarding Study IV, the adolescents.

Regarding study III, the Coordinating Ethics Committee of Helsinki and Uusimaa Hospital District approved the study, and the original study protocol was approved by the ethics committees of participating hospitals. Written informed consent was obtained from participants.

5 RESULTS

5.1 STUDY I – THE DOMAIN-SPECIFIC VULNERABILITIES IN COGNITION ARE ASSOCIATED WITH POOR OR SHORT SLEEP DIFFERENTLY IN BOYS AND GIRLS

We found several differences between girls' and boys' sleep quality and regularity, but not sleep duration: boys' sleep quality as measured by sleep efficiency, WASO, and fragmentation index was significantly poorer at 12 years of age (all p-values ≤0.01) whereas girls had more catch-up sleep than boys (p≤0.001).

There were no associations between intelligence and sleep duration or quality in girls. In other cognitive domains we found some associations, namely in tasks testing executive functioning. In girls, larger amounts of WASO and higher fragmentation index were associated with a higher number of Perseverative Errors in the WCST (B = 0.10, [95% CI 0.00, 0.20], p = 0.045; B = 0.30, [95% CI 0.05, 0.60], p = 0.021, respectively). In girls, longer weekend catch-up sleep was associated higher scores in the Similarities test (B = 2.32, [95% CI 0.23, 4.40], p = 0.03), and with longer reaction times in CPT (B = 2.45, [95% CI 0.32, 4.58], p = 0.025).

There were no associations between intelligence and sleep duration or quality in boys. The associations between boys' cognitive test performance and sleep duration, quality, and weekend catch-up sleep are presented in Table 2. Longer sleep duration was associated with longer reaction times in CPT (B = 4.81, [95% CI 1.50, 8.12], p < 0.001), higher D Prime scores (B = 3.76, [95% CI 0.51, 7.01], p = 0.024), and smaller amount of commission errors in CPT (B = -5.03, [95% CI -8.35, -1.71], p = 0.006).

Regarding sleep quality, higher sleep efficiency was associated with higher D Prime scores (B = 0.58, [95% CI 0.19, 0.94], p = 0.004), longer reaction times in CPT (B = 0.65, [95% CI 0.24, 1.06], p = 0.002), and a lower number of commission errors in CPT (B = -0.73, [95% CI -1.12, -0.33,], p < 0.001). Similarly, a higher fragmentation index was associated with poorer executive functioning (lower D Prime scores (B =-0.37, [95% CI -0.59, -0.14], p = 0.002), and a higher number of commission errors in CPT (B = 0.40, [95% CI 0.17, 0.63], p = 0.001), and, shorter reaction times (CPT B = -0.51, [95% CI -0.74, -0.27], p < 0.001). A larger amount of WASO minutes was associated with poorer executive functioning (lower D Prime scores (B =-0.13, [95% CI -0.22, -0.05], p = 0.002), shorter reaction times in CPT (B =-0.14, [95% CI -0.22, -0.05], p = 0.003), and a higher number of commission errors in CPT (B =0.13, [95% CI 0.05, 0.22], p = 0.003)).

Table 2. Associations between sleep and standardized T-scores from tests estimating intelligence, memory and executive functioning in 12-year-old boys.

	SLEEP DURATION		SLEEP EFFICIENCY		FRAGMENTATION INDEX		WASO		CATCH-UP SLEEP	
COGNITIVE DOMAIN	**B**	**(95 % CI)**	**B**	**(95 % CI)**	**B**	**(95 % CI)**	**B**	**(95 % CI)**	**B**	**(95 % CI)**
INTELLIGENCE (WISC-III)										
VOCABULARY	-0.96	(-4.18, 2.25)	-0.31	(-0.69, 0.07)	0.16	(-0.07, 0.39)	0.03	(-0.06, 0.11)	-0.10	(-2.13, 1.93)
SIMILARITIES	-1.86	(-5.14, 1.42)	-0.33	(-0.73, 0.07)	0.05	(-0.18, 0.29)	0.01	(-0.07, 0.10)	-1.12	(-3.16, 0.92)
PICTURE ARRANGEMENT	0.97	(-2.38, 4.32)	0.00	(-0.40, 0.40)	-0.05	(-0.29, 0.19)	-0.01	(-0.10, 0.07)	-0.81	(-2.91, 1.29)
BLOCK DESIGN	1.16	(-2.04, 4.36)	-0.05	(-0.43, 0.34)	0.01	(-0.22, 0.24)	-0.03	(-0.11, 0.05)	-1.13	(-3.10, 0.85)
VERBAL IQ	-1.41	(-4.22, 1.41)	-0.32	(-0.66, 0.02)	0.11	(-0.09, 0.31)	0.02	(-0.05, 0.09)	-0.61	(-2.37, 1.15)
PERCEPTUAL IQ	-1.07	(-1.64, 3.78)	-0.02	(-0.35, 0.30)	-0.02	(-0.21, 0.18)	-0.02	(-0.09, 0.05)	-0.97	(-2.65, 0.72)
OVERALL IQ	-0.44	(-3.56, 2.67)	-0.25	(-0.62, 0.13)	0.07	(-0.15, 0.30)	0.00	(-0.08, 0.08)	-1.08	(-3.01, 0.84)
MEMORY (NEPSY-II)										
NARRATIVE MEMORY	-0.23	(-3.60, 3.14)	-0.23	(-0.63, 0.18)	0.12	(-0.12, 0.36)	0.04	(-0.05, 0.12)	0.07	(-2.05, 2.19)
EXECUTIVE FUNCTIONS										
CPT										
OMISSIONS	0.40	(-2.64, 3.43)	0.14	(-0.23, 0.50)	-0.11	(-0.33, 0.10)	-0.04	(-0.12, 0.04)	-0.21	(-2.10, 1.68)
COMMISSIONS	-5.03*	(-8.35, -1.71)	-0.73*	(-1.12, -0.33)	0.40*	(0.17, 0.63)	0.13*	(0.05, 0.22)	-1.95	(-4.07, 0.16)
REACTION TIME	4.81*	(1.50, 8.12)	0.65*	(0.24, 1.06)	-0.51*	(-0.74, -0.27)	-0.14*	(-0.22, -0.05)	0.91	(-1.20, 3.01)
D PRIME	3.76*	(0.51, 7.01)	0.58*	(0.19, 0.97)	-0.37*	(-0.59, -0.14)	-0.13*	(-0.22, -0.05)	3.10*	(1.12, 5.08)
WCST										
PERSEVERATIVE ERRORS	-0.18	(-2.78, 2.43)	0.01	(-0.33, 0.34)	0.03	(-0.17,0.23)	0.02	(-0.06, 0.09)	0.50	(-1.14, 2.14)
TRIALS TO COMPLETE 1ST	-1.70	(-4.71, 1.32)	-0.01	(-0.39, 0.37)	-0.03	(-0.26, 0.19)	0.00	(-0.08, 0.08)	-0.29	(-2.20, 1.62)
TRAIL MAKING										
TRAIL MAKING RATIO	-0.22	(-1.86, 1.42)	-0.08	(-0.27, 0.12)	-0.05	(-0.17, 0.07)	0.00	(-0.04, 0.04)	0.26	(-0.75, 1.27)

All values adjusted for parental SES, BMI, pubertal development, and maternal glycyrrhizin consumption. Abbreviations: B = Unstandardized regression coefficients; 95 % CI = 95 % confidence intervals; WASO= Wake after sleep onset; WISC-III = Wechsler Intelligence Scale for Children III; NEPSY-II = Developmental Neuropsychological Assessment for Children II; CPT = Conners' Continuous Performance Test II; WCST = Wisconsin Card Sorting Task. Significance ($p<0.05$) marked *.

5.2 STUDY II – LONGITUDINAL SLEEP PLAYS A MORE PROFOUND ROLE IN LIPID PROFILE THAN RECENT SLEEP

In this study, we found significant differences between girls' and boys' sleep: girls sleep duration was longer at both measurement points (at 8 years and at 12 years of age) ($p \leq 0.01$) and their sleep quality was better ($p \leq 0.04$). Their lipid profiles were different regarding HDL-C and TGs, with boys having higher levels of HDL-C and girls having higher levels of TGs.

Table 3 presents the significant associations between sleep and lipids in girls. In boys the only significant association was found between longer sleep duration at 8 years and higher levels of TGs in Model 2, i.e. when controlling for age, BMI, physical activity, PDS, and SES (B = 0.38 [95% CI 0.08-0.69], p = 0.016).

When examining the associations between lipid profiles and change in sleep between the two measurement points, we found that a larger change in sleep duration lower levels of TC and LDL-C in girls and higher levels of TGs in boys. Also, in girls, a greater improvement in sleep quality as indicated by a smaller amount of WASO was associated with higher levels of TGs. In boys, a larger decrease in sleep duration was associated with higher TGs. The associations between change in sleep and lipid markers are illustrated in Figure 4.

Table 3. Associations between sleep and lipids in girls at ages 8 years and 12 years (standardized values).

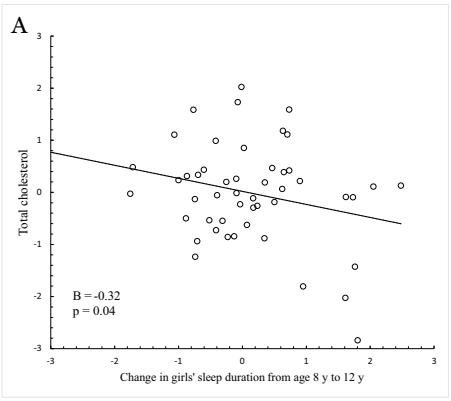
GIRLS' SLEEP	TC			LDL-C			HDL-C			TGs		
	B	(95 % CI)	p	B	(95 % CI)	p	B	(95 % CI)	p	B	(95 % CI)	p
DURATION, 8 Y												
MODEL 1	-0.16	(-0.49, 0.17)	**0.33**	-0.15	(-0.48, 0.18)	**0.36**	0.32	(0.03, 0.62)	**0.03**	-0.39	(-0.69, -0.09)	**0.01**
MODEL 2	-0.12	(-0.48, 0.23)	**0.49**	-0.12	(-0.48, 0.23)	**0.49**	0.31	(0.01, 0.62)	**0.04**	-0.36	(-0.68,-0.04)	**0.03**
WASO, 8 Y												
MODEL 1	0.20	(-0.10, 0.51)	**0.19**	0.08	(-0.23, 0.39)	**0.61**	-0.12	(-0.41, 0.17)	**0.40**	0.34	(0.06, 0.63)	**0.02**
MODEL 2	0.22	(-0.12, 0.55)	**0.20**	0.09	(-0.26, 0.43)	**0.62**	-0.12	(-0.42, 0.18)	**0.43**	0.33	(0.02, 0.64)	**0.04**
SLEEP EFFICIENCY, 8 Y												
MODEL 1	-0.20	(-0.52, 0.11)	**0.20**	-0.11	(-0.43, 0.22)	**0.51**	0.17	(-0.12, 0.47)	**0.25**	-0.39	(-0.68, -0.10)	**0.01**
MODEL 2	-0.21	(-0.57, 0.14)	**0.23**	-0.11	(-0.47, 0.25)	**0.53**	0.19	(-0.13, 0.50)	**0.24**	-0.39	(-0.71, -0.06)	**0.02**
CATCH-UP SLEEP, 8 Y												
MODEL 1	0.20	(-0.06, 0.46)	**0.13**	0.10	(-0.16, 0.37)	**0.43**	0.22	(-0.03, 0.46)	**0.08**	-0.17	(-0.42, 0.08)	**0.18**
MODEL 2	0.25	(-0.04, 0.53)	**0.09**	0.14	(-0.16, 0.43)	**0.36**	0.24	(-0.02, 0.50)	**0.07**	-0.17	(-0.45, 0.11)	**0.24**
DURATION, 12 Y												
MODEL 1	0.04	(-0.16, 0.25)	**0.68**	0.03	(-0.18, 0.23)	**0.79**	0.22	(0.01, 0.42)	**0.04**	-0.19	(-0.40, 0.02)	**0.08**
MODEL 2	-0.02	(-0.24, 0.21)	**0.89**	0.00	(-0.22, 0.22)	**0.99**	0.18	(-0.04, 0.39)	**0.11**	-0.19	(-0.43, 0.04)	**0.11**
WASO, 12 Y												
MODEL 1	0.01	(-0.18, 0.20)	**0.94**	-0.09	(-0.28, 0.10)	**0.34**	0.02	(-0.18, 0.21)	**0.87**	0.10	(-0.09, 0.30)	**0.30**
MODEL 2	0.06	(-0.15, 0.26)	**0.58**	-0.03	(-0.23, 0.17)	**0.79**	-0.02	(-0.22, 0.17)	**0.83**	0.16	(-0.06, 0.37)	**0.15**
SLEEP EFFICIENCY, 12 Y												
MODEL 1	0.04	(-0.16, 0.23)	**0.72**	0.13	(-0.06, 0.32)	**0.18**	-0.02	(-0.23, 0.18)	**0.82**	-0.06	(-0.27, 0.14)	**0.53**
MODEL 2	0.01	(-0.20, 0.21)	**0.94**	0.10	(-0.10, 0.30)	**0.34**	-0.01	(-0.20, 0.19)	**0.95**	-0.09	(-0.31, 0.12)	**0.40**
CATCH-UP SLEEP, 12 Y												
MODEL 1	0.10	(-0.11, 0.31)	**0.35**	0.08	(-0.13, 0.29)	**0.46**	-0.04	(-0.24, 0.17)	**0.74**	0.24	(0.03, 0.46)	**0.02**
MODEL 2	0.10	(-0.11, 0.31)	**0.33**	0.06	(-0.15, 0.27)	**0.56**	0.01	(-0.18, 0.20)	**0.89**	0.21	(0.00, 0.42)	**0.05**

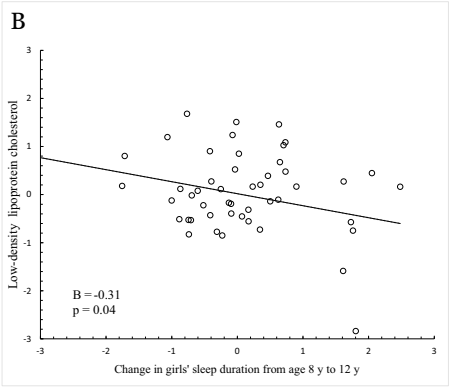
Abbreviations: B=regression coefficient; WASO=wake after sleep onset; BMI=body mass index; TC=Total Cholesterol; LDL-C=low-density lipoprotein cholesterol; HDL-C= high-density lipoprotein cholesterol; TGs= Triglycerides; y=years

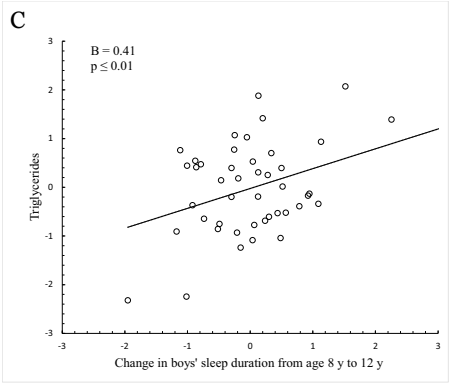
Model 1 – adjusted for age at 12 y

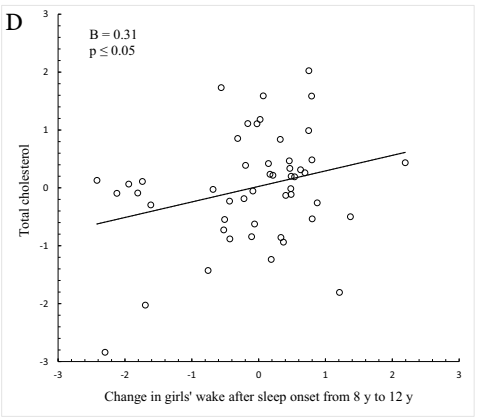
Model 2 – adjusted for age, BMI, Physical Activity, Pubertal Development, Socio-economic status (measured at 12 years)

Figure 4. Significant associations between lipids and change in sleep duration (panels A-C) and in wake after sleep onset (panel D) from age 8 to 12 years.









5.3 STUDY III – EXECUTIVE FUNCTIONING AND SLEEP BEHAVIOUR IN YOUNG ADULTS

Table 4 presents the associations between sleep and EFs as continuous scores. In both Model 1 and Model 2, longer sleep duration was associated with less commission errors (CPT) and better attentiveness, but longer reaction times. In both Model 1 and Model 2, later sleep midpoint was associated with higher scores in GEC and MI, indicating poorer self-reported EF. Later sleep midpoint was also associated with faster performance time in both parts of the Trail making test, but these associations did not survive adjustments in Model 2. Greater variability in sleep duration was associated with more commission errors and lower D prime scores.

The categorical division of sleep variables showed a similar pattern as the continuous scores. Figure 5 illustrates the mean differences in EF scores between the different thirds of sleep: shortest sleep duration thirds versus other thirds, the longest sleep duration third versus others, the most irregular sleep third versus other thirds, and, the latest sleep midpoint third versus other thirds. The short duration third made more commission errors ($p = 0.038$) and lower D prime score ($p = 0.047$). The longest sleep duration third made fewer commission errors ($p = 0.035$). The most irregular sleep third had slower trail making performance in part A ($p = 0.04$) and lower ratio score ($p = 0.029$). The latest sleep midpoint third had highest MI, BRI and GEC scores in BRIEF ($p < 0.001$; $p = 0.042$ and $p < 0.001$, respectively, but faster performance in trail making test part B ($p = 0.030$).

Those categorized as having both late circadian rhythm and short sleep duration ($n = 44$) had poorer trait-like EF compared to the rest of the sample in all three BRIEF measures: they had higher GEC scores [MD (95% CI) 4.34 (0.80, 7.87); $p = 0.017$], higher MI scores [MD (95% CI) = 4.46 (0.80, 8.11); $p = 0.017$], higher BRI scores [MD (95% CI) 3.53 (0.18, 6.88);$p = 0.035$]. Those categorized as having both late circadian rhythm and long sleep duration ($n = 79$) differed from the others in three respects: they made less commission errors [MD (95% CI) 2.71 (5.21, 0.22); $p = 0.033$], had higher MI scores [MD (95% CI) 4.04 (1.15, 6.93); $p = 0.006$] and higher GEC scores [MD (95% CI) 3.59 (0.73, 6.44); $p = 0.014$].

Table 4. Associations between sleep measurements and executive function.

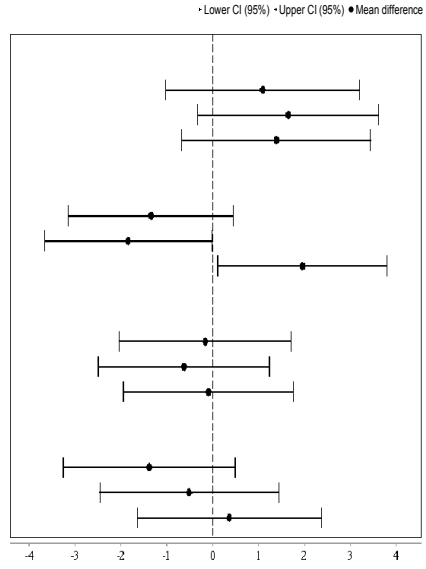
	SLEEP DURATION			MIDPOINT			VARIATION IN SLEEP		
	B	(95% CI)	p	B	(95% CI)	p	B	(95 % CI)	p
BRIEF-A									
GLOBAL EXECUTIVE									
MODEL 1	-0.05	(-0.15, 0.05)	**0.36**	0.16	(0.06, 0.26)	**0.002**	0.03	(-0.09, 0.15)	**0.66**
MODEL 2	-0.03	(-0.13, 0.07)	**0.56**	0.16	(0.05, 0.26)	**0.003**	-0.01	(-0.13, 0.11)	**0.84**
BEHAVIORAL									
MODEL 1	-0.05	(-0.15, 0.05)	**0.30**	0.10	(-0.01, 0.19)	**0.06**	-0.01	(-0.13, 0.10)	**0.82**
MODEL 2	-0.03	(-0.13, 0.07)	**0.56**	0.09	(-0.01, 0.19)	**0.08**	-0.06	(-0.17, 0.06)	**0.31**
METACOGNITION									
MODEL 1	-0.04	(-0.14, 0.06)	**0.44**	0.18	(0.08, 0.29)	**<0.001**	0.05	(-0.07, 0.17)	**0.44**
MODEL 2	-0.03	(-0.13, 0.07)	**0.58**	0.18	(0.08, 0.29)	**<0.001**	0.02	(-0.11, 0.14)	**0.79**
CPT									
COMMISSIONS									
MODEL 1	-0.15	(-0.24, -0.05)	**<0.001**	-0.06	(-0.16, 0.04)	**0.24**	0.17	(0.04, 0.29)	**0.01**
MODEL 2	-0.12	(-0.22, -0.03)	**<0.001**	-0.06	(-0.17, 0.04)	**0.22**	0.14	(0.02, 0.27)	**0.03**
REACTION TIME									
MODEL 1	0.09	(0.00, 0.18)	**0.05**	0.03	(-0.07, 0.12)	**0.62**	-0.13	(-0.26, 0.00)	**0.05**
MODEL 2	0.10	(0.01, 0.19)	**0.03**	0.02	(-0.08, 0.12)	**0.64**	-0.13	(-0.26, 0.00)	**0.05**
D PRIME									
MODEL 1	0.13	(0.03, 0.22)	**0.01**	0.10	(0.00, 0.20)	**0.05**	-0.17	(-0.30, -0.05)	**0.01**
MODEL 2	0.10	(0.01, 0.20)	**0.03**	0.10	(0.00, 0.20)	**0.05**	-0.16	(-0.28, -0.03)	**0.01**
TRAIL MAKING									
PART A									
MODEL 1	-0.02	(-0.11, 0.07)	**0.64**	-0.11	(-0.21, 0.00)	**0.04**	0.07	(-0.05, 0.20)	**0.23**
MODEL 2	0.00	(-0.09, 0.09)	**0.99**	-0.09	(-0.19, 0.01)	**0.08**	0.07	(-0.06, 0.19)	**0.28**
PART B									
MODEL 1	-0.02	(-0.12, 0.07)	**0.60**	-0.11	(-0.21, -0.01)	**0.04**	0.02	(-0.10, 0.14)	**0.73**
MODEL 2	0.02	(-0.07, 0.12)	**0.64**	-0.10	(-0.20, 0.00)	**0.05**	0.00	(-0.12, 0.13)	**0.96**
RATIO									
MODEL 1	-0.01	(-0.10, 0.08)	**0.77**	0.01	(-0.09, 0.11)	**0.88**	-0.04	(-0.16, 0.08)	**0.54**
MODEL 2	0.01	(-0.09, 0.10)	**0.90**	-0.01	(-0.11, 0.10)	**0.92**	-0.05	(-0.17, 0.07)	**0.44**
STROOP									
PART 1									
MODEL 1	0.00	(-0.09, 0.10)	**0.95**	-0.06	(-0.16, 0.05)	**0.30**	-0.04	(-0.15, 0.08)	**0.54**
MODEL 2	0.05	(-0.04, 0.15)	**0.27**	-0.05	(-0.15, 0.05)	**0.34**	-0.05	(-0.17, 0.07)	**0.41**
PART 2									
MODEL 1	0.00	(-0.09, 0.10)	**0.93**	-0.04	(-0.14, 0.07)	**0.53**	-0.02	(-0.14, 0.10)	**0.76**
MODEL 2	0.05	(-0.04, 0.15)	**0.27**	-0.03	(-0.13, 0.08)	**0.64**	-0.06	(-0.18, 0.06)	**0.34**
INTERFERENCE									
MODEL 1	0.00	(-0.09, 0.10)	**0.94**	0.00	(-0.11, 0.11)	**0.95**	0.00	(-0.12, 0.13)	**0.98**
MODEL 2	0.03	(-0.07, 0.13)	**0.53**	0.01	(-0.11, 0.12)	**0.93**	-0.04	(-0.17, 0.09)	**0.53**

Abbreviations: B=regression coefficient; BMI=body mass index; BRIEF-A= Behavior Rating Inventory of Executive Function; CI= confidence interval; CPT= Conners' Continuous Performance Test II.
Model 1 – adjusted for sex and age
Model 2 – adjusted for sex, age, BMI, and socio-economic status

Figure 5. Mean differences (MD) in executive functioning between specific sleep behaviour tertiles and others.

A. Shortest sleep duration tertile versus others

EXECUTIVE FUNCTION MEASURE	
BRIEF-A	**MD**
Metacognition index	1.08
Behavioral Regulation Index	1.64
Global Executive Composite	1.38
Continuous Performance Test	
Reaction time	-1.35
D Prime	-1.85
Commission errors	1.95
Trail making test	
Part A, time	-0.17
Part B, time	-0.63
Ratio score	-0.10
Stroop	
Part 1 (baseline)	-1.39
Part 2	-0.52
Interference score	0.35



B. Longest sleep duration tertile versus others

EXECUTIVE FUNCTION MEASURE	
BRIEF-A	**MD**
Metacognition index	0.72
Behavioral Regulation Index	0.78
Global Executive Composite	0.81
Continuous Performance Test	
Reaction time	1.53
D Prime	1.70
Commission errors	-1.98
Trail making test	
Part A, time	-0.19
Part B, time	0.53
Ratio score	0.41
Stroop	
Part 1 (baseline)	0.78
Part 2	0.52
Interference score	0.10

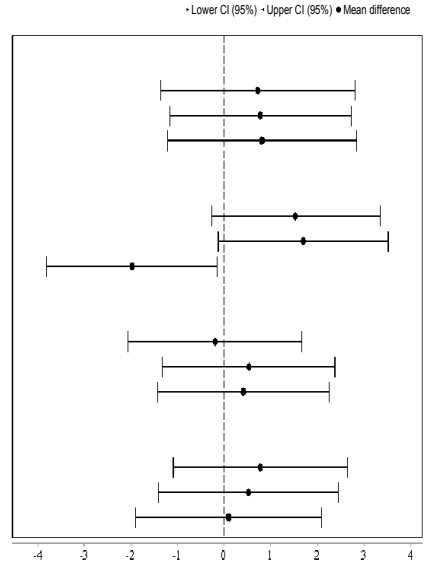
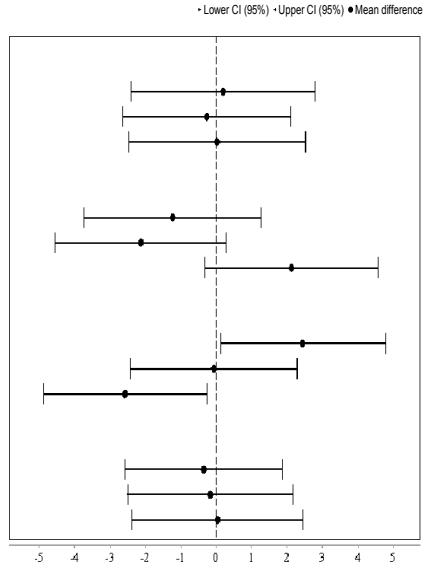


Figure 5, continued

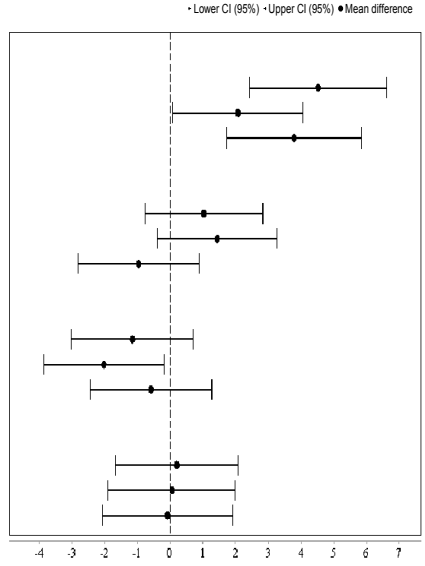
C. Highest variation in duration tertile versus others

EXECUTIVE FUNCTION MEASURE	
BRIEF-A	MD
Metacognition index	0.19
Behavioral Regulation Index	-0.27
Global Executive Composite	0.02
Continuous Performance Test	
Reaction time	-1.23
D Prime	-2.13
Commission errors	2.12
Trail making test	
Part A, time	2.45
Part B, time	-0.07
Ratio score	-2.58
Stroop	
Part 1 (baseline)	-0.35
Part 2	-0.17
Interference score	0.04



D. Latest midpoint tertile versus others

EXECUTIVE FUNCTION MEASURE	
BRIEF-A	**MD**
Metacognition index	4.52
Behavioral Regulation Index	2.07
Global Executive Composite	3.79
Continuous Performance Test	
Reaction time	1.03
D Prime	1.44
Commission errors	-0.97
Trail making test	
Part A, time	-1.16
Part B, time	-2.03
Ratio score	-0.59
Stroop	
Part 1 (baseline)	0.20
Part 2	0.05
Interference score	-0.09



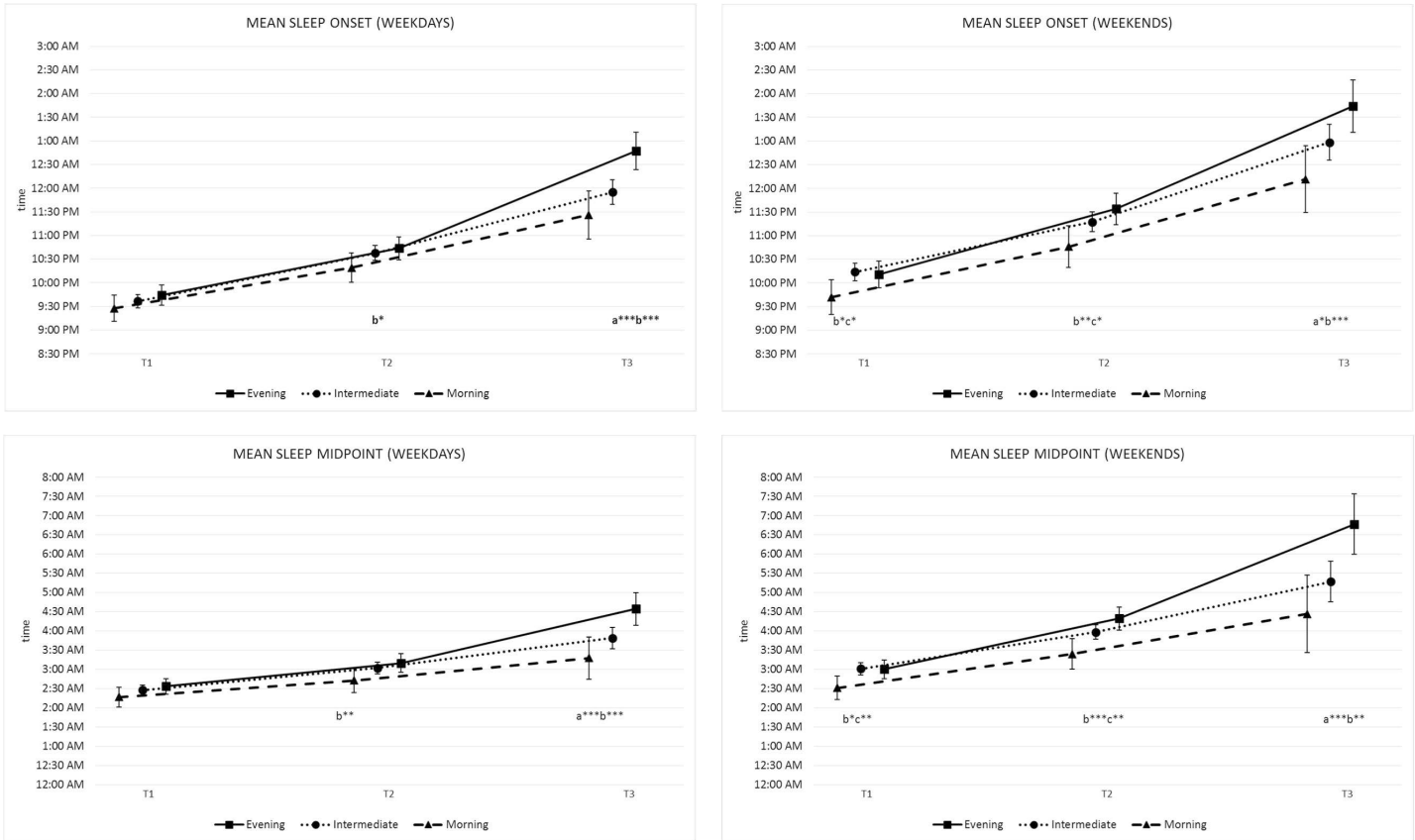
5.4 STUDY IV – THE DEVELOPMENT OF SLEEP TIMING FROM MIDDLE CHILDHOOD TO ADOLESCENCE FROM A CIRCADIAN PREFERENCE PERSPECTIVE

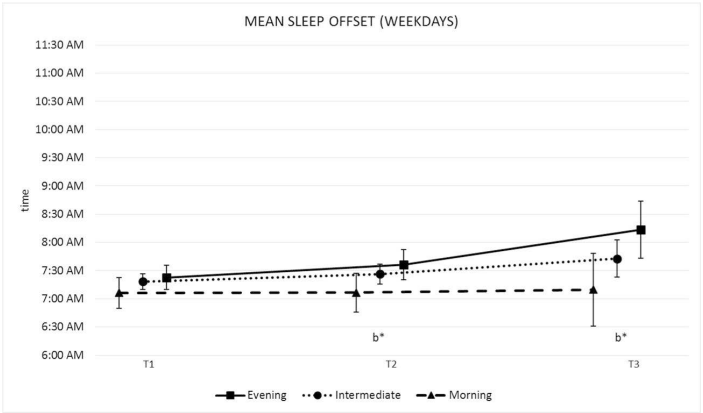
In this study, we investigated the development of sleep behaviour over three measuring points, covering nine years from middle childhood to adolescence. We found no health- or development-related differences between circadian preference groups when investigating birth weight, socioeconomic status, BMI at different follow-ups, or, PDS at 12 years or 17 years. Also, we found no significant sex or age differences between circadian preference groups.

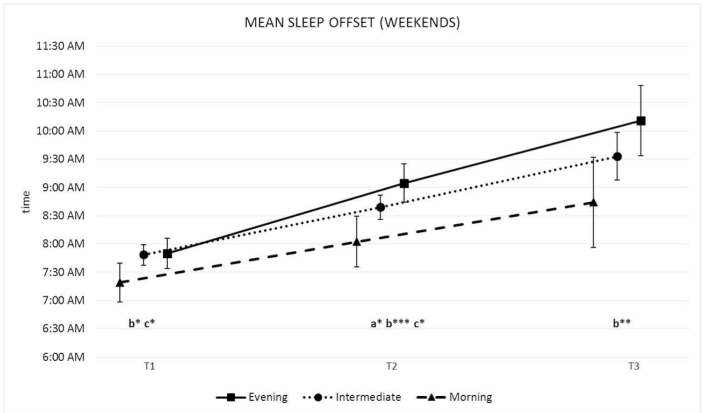
Overall development in sleep followed the lines of previously published reports (Crowley et al., 2014; Pesonen et al., 2014): weekday and weekend sleep duration decreased over the three measurement points, WASO decreased, sleep efficiency increased. Regarding sleep regularity, the amount of weekend catch-up sleep increased over three measurement points, and, regarding sleep timing, sleep onset and sleep offset times shifted to later. This was also reflected in later sleep midpoints on both weekdays and weekends.

Mixed model analyses showed that 1 interval toward morningness changed the overall mean of sleep midpoint on all days (B = -23.82 minutes, [95% CI -32.87, -14.77], $p < .001$), weekdays (B = -24.20 minutes, [95% CI -35.74, -12.66], $p < .001$), and weekends (B = -35.81 minutes, [95% CI -54.58, -17.04], $p < .001$). This was reflected also in sleep onset, (B = -20.89 minutes, [95% CI -29.80, -11.98], $p < .001$; B = -27.61 minutes, [95% CI -40.79, -14.44], $p < .001$, respectively) and offset (B = -17.54 minutes, [95% CI -28.04, -7.04], $p \leq .001$; B = -28.87 minutes, [95% CI -42.83, -14.91], $p < .001$, respectively) on both weekdays and weekends, respectively. The greatest change in sleep timing occurred from age 12 to 17, and was most profound in the evening types. We found no differences in sleep duration, wake after sleep onset, sleep efficiency, or catch-up sleep between circadian preference phenotypes. Figure 6 illustrates the differences in significant sleep timing variables between circadian preference groups over the three measurement points.

Figure 6. Development of sleep timing over nine years according to circadian preference. Mean measures of sleep onset, midpoint, and offset at Time point 1 at 8 years of age (T1), Time point 2 at 12 years of age (T2), and Time point 3 at 17 years of age (T3) according to circadian preference at age 17. Bars represent 95 % confidence intervals. Mean difference significance marked: a=evening vs. intermediate type; b=evening vs. morning type; c=intermediate vs. morning type; *p<.05, **p<.01 ***p<.001.




MEAN SLEEP OFFSET (WEEKDAYS)
time
11:30 AM
11:00 AM
10:30 AM
10:00 AM
9:30 AM
9:00 AM
8:30 AM
8:00 AM
7:30 AM
7:00 AM
6:30 AM
6:00 AM
b*
b*
T1
T2
T3
Evening
Intermediate
Morning


MEAN SLEEP OFFSET (WEEKENDS)
time
11:30 AM
11:00 AM
10:30 AM
10:00 AM
9:30 AM
9:00 AM
8:30 AM
8:00 AM
7:30 AM
7:00 AM
6:30 AM
6:00 AM
b* c*
a* b*** c*
b**
T1
T2
T3
Evening
Intermediate
Morning

6 DISCUSSION

6.1 STUDY I

Studies investigating specific cognitive domains, and how habitual sleep behaviour relates to these domains, are sparse, especially in children and adolescents.

In this study, boys' habitual sleep was associated with poorer executive function, namely as fast but error-prone performance. These findings may either suggest that at this point of development, sleep among boys has a stronger influence on cognitive performance than among girls, or, that boys' sleep is not sufficient to begin with. Both explanations are likely to reflect sexual dimorphisms stemming from neural and/or behavioural differences.

In order to adjust for some differences in maturation, we controlled for pubertal development, which may explain some of the differences reported in this age group. However, the physical markers of pubertal development may have later onset than neural maturation and may not detect the state of neural development accurately. Executive function has a strong neural basis, mainly in prefrontal cortex which also regulates sleep. The prefrontal regions in the developing brain are particularly vulnerable for sleep deprivation. Due to the shorter sleep duration in boys, it can be speculated that, in boys, a naturalistic sleep deprivation setting is already present in this sample. However, on an epidemiological level, females are shown to sleep longer (Anderson & Horne, 2008; Groeger, Zijlstra, & Dijk, 2004), which may stem from higher sleep need, or a reporting bias.

Regularity of sleep duration over weekdays and weekends had some, but incoherent, associations with executive functioning and intelligence, with longer catch-up sleep being associated with higher verbal intelligence and longer reaction times in girls, and better attentiveness in boys. Previous reports in adolescent sleep have not addressed the relationship between catch-up sleep and intelligence. As our participants are in early adolescence, and the only association regarding intelligence was specifically in verbal performance, our finding is likely to stem from behavioural differences, such as choosing to read a book before going to bed, rather than obtaining too little sleep on school nights due to going to parties. The finding in boys is not in line with previous studies which have suggested an increasing effect of sleep irregularity on omission and commission errors among Korean adolescents (Kim et al., 2011). However, in our sample, the mean level difference between weekend and weekday sleep was less than half an hour in our sample, whereas in the Korean study the difference was almost 2.5 hours. Thus, the measure may reveal different aspects in different samples, and

using an improved index of sleep duration irregularity may be useful in future studies (Rowe et al., 2008).

Some studies and theories have suggested that intelligence might play a part in executive functioning (Blair, 2006). In order to investigate this, data were re-analysed and controlled for estimated IQ. We found no significant changes in the associations, and conclude that those elements in EF measuring tests which suffer as a result of poor sleep, are not driven by general intelligence. In further investigations, we also ran the analyses with only school night sleep measurements and found that all significant results remained, implying that even school nights, which typically have bedtimes influenced by parental guidance, differentiate between sufficient and insufficient sleep.

Our findings are in line with previous reports regarding sleep deprivation studies in EF (Jackson et al., 2013; Rossa et al., 2014), and some studies investigating associations between sleep and intelligence in children (Nixon et al., 2008). Based on the null findings in both girls' and boys' intelligence and sleep, it would seem that intelligence is not affected by sleep even when other cognitive domains suffer in association with insufficient or poor sleep. It may well be that the source of the decline in the tests we used to measure EF is mostly in the non-executive cognitive components of the tasks.

Various previous studies have found associations between memory and sleep. In our study, we did not detect any significant association between sleep duration, quality, or, regularity and the narrative memory task performance. Hence, it is likely that performance in the narrative memory task taps on cognitive abilities that are not sensitive to sleep, or, that the participants' sleep was sufficient during the measurement period (ranging from 6.5 to 10.9 hours).

Previous studies have suggested that adolescents' cognitive performance gets impaired due to insufficient sleep (Beebe, 2011). The majority of studies investigating the effects of insufficient sleep have used partial or total sleep deprivation settings. Restricted sleep is prevalent in most modern societies: approximately 30 percent of adults (30–40%), school aged children (31%), and adolescents (26%) report shorter sleep durations than age-appropriate recommendations (Chaput & Janssen, 2016; "Effect of short sleep duration on daily activities--United States, 2005-2008," 2011; Hirshkowitz et al., 2015). This suggests a considerable risk for insufficient sleep across all age groups, and, as our findings suggest, everyday cognitive functions such as attentiveness may suffer in association.

In a community-based, non-clinical, full-term sample it is likely that habitual sleep is not a risk factor for scoring poorer in intelligence tests. When children are healthy, it may well be that their naturally occurring individual sleep covers what is necessary for their adequate cognitive functioning, even though some measures suggest poorer performance (Geiger, Achermann, & Jenni, 2010b).

6.2 STUDY II

In study II, we found that sleep duration and poorer sleep quality in middle childhood were associated with lipid profile in early adolescence. The associations between sleep and lipids were strongest when observing sleep longitudinally, over a 4-year follow-up period, and especially in girls. This suggests that lipids and sleep are related longitudinally before full adolescence. We additionally detected cross-sectional associations in girls, but found that the longitudinal associations were even more profound.

The finding regarding sleep duration and lipids are in line with previous cross-sectional studies (Azadbakht et al., 2013; Spruyt et al., 2011), and one longitudinal study using self-reported sleep duration (Cespedes et al., 2014). The differences between girls and boys have also been reported in relation to lipids (Berentzen et al., 2014). We found that in girls, longer and better quality sleep was associated positively with cholesterol markers, whereas in boys, we only detected one associations, which only became significant after controlling for age, PDS, BMI, socioeconomic status, and, physical activity. Regarding the associations between sleep change and lipids, we suggest that normative change in sleep duration and quality during the transition from childhood to adolescence has a beneficial effect on lipid profiles in girls, manifested as lower TC and lower LDL-C. In cross-section, we found that longer catch-up sleep in early adolescence was associated with higher TGs in girls. Previous studies have reported that weekend catch-up sleep may have some beneficial effects on metabolic markers, which contradicts our findings (Spruyt et al., 2011; Wing, Li, Li, Zhang, & Kong, 2009).

Sleep and metabolism are intertwined. TGs, which may further transform into LDL-C, are highly sensitive to food intake, and as sleep deprivation affects appetite, it is possible that longitudinal insufficient sleep, or irregularity in sleep patterns, leads to unhealthy dietary choices and increased appetite. Based on our longitudinal findings, and previous reports on inhibition and risk-taking, it is possible that insufficient sleep has an adverse effect on self-control, which reflects on choices a person makes during wake. This nocturnal programming hypothesis suggests that night-time sleep may be associated with risk of diseases later in life.

A recent study described the potentially shared molecular mechanism which ties together the metabolism of lipids, and sleep duration (Ollila et al., 2012). The authors found evidence that the gene expression of TRIB1 was regulated by sleep duration and deprivation, and that it is associated with metabolic outcomes such as HDL-C, LDL-C, and TGs. It is likely that some of the findings in our study are related to this mechanism.

6.3 STUDY III

In study III, we found different associations between sleep and self-reported EF versus performance-based test scores in young adults. Sleep timing, namely later sleep midpoint, was associated with weaker EF, whereas sleep duration was associated with poorer performance in tests measuring EFs. Additionally, variation in sleep duration was associated with weaker EF test performance. Sleep deprivation studies have demonstrated the effects of short sleep duration on EFs (Jackson et al., 2013; Lowe et al., 2017; Slama et al., 2017), though some studies also report only minor effects (Tucker et al., 2010). Based on the studies reporting weaker EF as a result of sleep deprivation, our findings regarding sleep duration and the performance-based EF scores were expected, and similar to those reported in study I.

The mechanism behind the associations between sufficient sleep duration and EFs is likely to relate to the benefits of certain aspects of sleep (i.e. amount of slow-wave sleep) on prefrontal cortex function. Gaining a sufficient duration of sleep allows full cycles of different sleep stages to emerge. This may in turn benefit cognitive processes, such as EFs which are dependent on the prefrontal cortex, and associated neural networks (Wilckens, Erickson, & Wheeler, 2012). This mechanism would explain how individual differences in sleep result in below optimal performance in tasks requiring working memory, inhibition, and, controlled memory processes while lower level aspects, such as process speed, remain less affected.

In addition to the sleep duration findings we also report sleep timing and its associations with EF. Our main findings relate to BRIEF, which evaluates different aspects of executive control. The significant associations we found may stem from circadian regulation, with later circadian preference being associated with poorer self-control and procrastination (Digdon & Howell, 2008). However, no causality can be detected: subjective reports of executive function may also reflect a subjective experience of one's ability to go to sleep at an appropriate and socially acceptable time. "Early to bed, early to rise, keeps a man healthy, wealthy and wise" is a socially accepted perspective on everyday circadian rhythms, and a preference for a later rhythm may be perceived as poor self-regulation, thus resulting in higher BRIEF scores from those with eveningness preference. This view is partially supported by the differentiated effect of sleep duration on EFs in our study, and a previous study in adolescents, which found no effect of sleep duration on BRIEF-derived self-regulation scores, but a significant association with poorer self-regulation and both preference for eveningness, and daytime sleepiness (Owens et al., 2016).

Based on this study, it seems plausible to assume that shorter sleep duration may be associated with poorer cognitive performance in EF tasks, whereas later sleep timing is more associated with overall, trait-like executive functioning.

6.4 STUDY IV

In study IV we investigated how the adolescents' preference for eveningness develops from middle childhood onwards. We found that overall sleep timing became later over the three follow-ups, which is in line with previous literature regarding later sleep phase in adolescence (M. A. Carskadon, 2011; M. A. Carskadon et al., 1998; Crowley et al., 2014; Hagenauer, Perryman, Lee, & Carskadon, 2009). However, most theories suggest that later chronotype emerge as a pubertal element (Hagenauer et al., 2009; Roenneberg et al., 2004), whereas our data indicate that sleep timing during weekends differed significantly between circadian preference groups already at 8 years of age. Weekend sleep timing was different between morning and evening types during all measurement points. These findings were in line with our initial hypothesis.

We found that sleep duration did not differ across circadian preference types, which was against our hypothesis, and not in line with previous cross-sectional studies which report shorter sleep duration in those with a preference for eveningness (Allebrandt et al., 2014; Kitamura et al., 2010). However, previous studies have mostly used self-reported sleep duration as a measure, which may explain some of the discrepancy. Sleep quality did not differ between different circadian preference groups, though some previous studies using subjective measurements have reported differences between groups (Vollmer et al., 2017).

Previous research has described the concepts of Process C and Process S as central constructs of sleep behaviour. As theoretical constructs these are considered separate, but from a practical viewpoint, they overlap and create an intertwined rhythm which manifests as habitual sleep. In our study, we were able to detect sleep patterns over nine years from middle childhood to adolescence, and detected differences between morning and evening types already at 8 years of age. As we found not differences in sleep duration, quality, or, catch-up sleep, it seems possible that the circadian processes are separate and may act as primus motor in the interaction between process C and process S. This finding is in line with the general assumption of the SCN being the central circadian pacemaker.

One previous study in children reported poor sleep stability in 3- to 7-year-olds, with less than 15 % of the participants being classified as having stable sleep behaviour (Taylor, Williams, Farmer, & Taylor, 2015). This finding may be a result of mixed ethnic variation, which was not present in our study sample.

The genetic foundation of sleep timing plays a part in actualized sleep behaviour in adults, but in children and during early adolescence sleep

timing is likely to be influenced by parental control. During weekends individual preferences have more possibilities to emerge, as schedules are likely to be more flexible.

6.5 METHODOLOGICAL CONSIDERATIONS

Although actigraphy is solely a measure of movement (or, acceleration), the measures that are derived from it may reflect some aspects of EEG: sleep stages need a sufficient time to build up during the night. An estimated 90 minutes should be reserved for one cycle to develop through N1, N2, N3, and REM. Thus, fragmented sleep may disturb the natural architecture of sleep, and, similarly, short sleep duration may prohibit the formation of a sufficient cumulative amount of different sleep stages. Actigraphy is a sufficient tool for investigating sleep duration and timing, but in comparing healthy adolescents' sleep it may not reveal enough details in order to detect the elements which influence cognitive functioning. This differentiation requires PSG, or sleep EEG.

While the tests we have used in estimating the cognitive performance in adolescents and young adults have been validated, some criticism has also been put forward in the tests' abilities to detect specific cognitive functions. The WCST may not be an accurate measure of prefrontal performance as such (Nyhus & Barcelo, 2009), but measures maturation and a broad range of cognitive abilities.

Study I included a large battery of cognitive tests, and while most of the associations in boys' EF test performance and sleep were evident, other cognitive domains we measured did not show any associations with sleep. However, not all domains, such as working memory, were investigated. The scores we report focus on either trait-like or state-like features of cognitive processes, and the tests performed under strict laboratory surroundings do not necessarily have high ecological validity: performance-based EF tests lack real-world significance. Additionally, none of the tests presented in this study reflect dynamic, higher level cognition. The only memory test we included in this study was Narrative memory, which evaluates learning and remembering new facts, and is thus thought to be a measurement of specific declarative verbal memory and the ability to sustain auditory attention. While we did not find any significant associations between habitual sleep and memory performance in this task, previous studies with sleep restriction protocols have found decline in test performance in various memory tasks.

In order to evaluate memory and learning in a more detailed context, after the 12-year-olds' follow-up, we executed a more dynamic approach to investigate the same adolescents when they were 17 years old. We tested the

adolescents' learning abilities and they underwent a thorough sleep study including overnight PSG and 8-10-day actigraphy measurements. The results are currently being processed.

In study I, we focused on sleep duration and quality, and used weekend catch-up sleep as a measure of sleep regularity and sleep debt. Sleep timing was not reported in this study, which may convey some associations. As many studies emphasize the importance of circadian preference, circadian phase, and chronotype over cognitive domains, I re-analysed the data using weekend sleep midpoint as a predictor of cognitive performance, and found no significant associations (data not presented). Additionally, out of interest, I compared 12-year EF performance between circadian preference groups measured at 17 years, but found no significant differences (data not presented). Hence, in this study, it would seem that in early adolescence sleep quality and duration are the most important sleep measures which are associated with optimal EF performance.

The setting in study II enabled the observation of two measurement points of sleep, but only one measurement of lipid levels. Thus, it was not possible to investigate the development of lipids over time. Additionally, nutrition was not controlled in this study – it may be the mediating mechanism between sleep and lipids (Hart et al., 2013).

Study II focused on sleep duration, quality, and weekend catch-up sleep, and did not take into consideration the circadian elements of sleep. While this is a separate research question, I re-ran the analyses in order to detect the significant associations between lipid levels and sleep timing, namely weekend midpoint in childhood and early adolescence. There were no significant associations (data not presented).

As both longer and shorter sleep duration have been associated with unfavourable health outcomes (Cappuccio, Cooper, D'Elia, Strazzullo, & Miller, 2011), we tested the statistical significance of a quadratic term added in addition to the linear term as a predictor in the model. However, in our sample, there were no significant curvilinear associations between sleep duration and any of the lipids (data not presented).

In study III, the pre-term individuals in the data set were excluded due to a priori assumption of profound differences in both sleep timing (Bjorkqvist et al., 2014) and EF (Strang-Karlsson et al., 2010; Strang-Karlsson et al., 2008). Another approach would have been to include them, and then control for gestation weeks in order to detect the effects of gestation age within the same study.

This study reports findings from both self-reported EF and performance-based scores. The reported associations were different between self-reports and performance: self-reported EF was mainly associated with sleep timing, suggesting either a specific but generalized vulnerability to later circadian rhythm, or, an association involving weaker self-observed self-regulation in those with later sleep timing. Our study does not offer any insight into the

causality of this association due to the cross-sectional nature of the study setting.

Regarding methodological considerations in study IV, some issues may be pointed out. Due to missing data, the scale selected for this study was a reduced version modified from the original MEQ, which is not optimal. However, the reduced scale was developed in a Finnish population and thus may acknowledge cultural aspects of the trait-like aspects of morningness-eveningness.

Some of our results are likely to be explained by the genetic basis of circadian preference, which was not investigated in this study. A previous study in Finnish twins has suggested heritability explaining approximately 50 % of preference for morningness/eveningness (Koskenvuo, Hublin, Partinen, Heikkila, & Kaprio, 2007), likely suggesting a moderate genetic component also in singletons.

A further improvement for the setting in this study would have included a morningness/eveningness questionnaire already in childhood – the longitudinal data only contained actigraphy data, which limits the possibilities to investigate MEQ score as a stable trait in this population.

All the studies in this thesis were conducted in Finnish participants living in the Finnish society and cultural surroundings. The socio-economic status of our participants is high compared to most of the world, and the ethnicity of the sample was completely homogeneous, which raises the question of generalisation of these results.

Finally, due to the correlational nature of cross-sectional studies, no causality is assumed in interpreting the results.

7 GENERAL DISCUSSION

Study I found that intelligence and memory performance were not associated with habitual short or poor quality sleep. A larger amount of catch-up sleep seemed to imply higher intelligence in girls' verbal ability tests, as well as better attentiveness in boys, which was likely due to the extra sleep the children were getting during weekend rather than shorter sleep during weekdays, or, behavioural differences in those girls with better verbal abilities.

Previous experimental studies have concluded that sleep deprivation causes a decline in executive functioning. This was also the case in studies I and III, which included tests measuring EF performance. All the studies in this thesis were non-experimental sleep studies with no manipulation of naturally occurring sleep behaviour, hence, smaller effects were expected and detected than those reported in sleep deprivation studies.

No previous study in healthy adults has addressed whether the more stable, trait-like features of EF are associated with sleep, and how performance-based EF is associated with sleep behaviour within the same study. In response to the potentially insufficient measure of sleep regularity in study I, an improved measure of sleep duration variability was included in Study III (Rowe et al., 2008). We detected poorer attentiveness and a more error-prone response style in those with greater variation in sleep duration. While this finding may also be related to findings in shorter sleep duration, it takes into account the amount of variation manifested over the measurement period. This provides extra information which may be a more efficient measure of circadian stability than investigating sleep midpoint in isolation.

As sleep is also closely linked to health risks, Study II utilized the available longitudinal data in observing the long-term associations between sleep and serum lipids. Previous research in this field has focused mainly on those with some risks already present in their metabolism (i.e. overweight or obese individuals). Our results were similar in direction, but we found that even in healthy children within a normal weight range, and even after adjusting for physical activity, BMI, and other covariates, the child's previous sleep behaviour four years prior to the lipid measurements, remains significantly associated with lipid levels in the child's blood. The sleep measurements described in this thesis are aimed at covering a typical period in the participants' lives, so it is likely that the mean-level measurements reflect an even longer time period than measured.

The goal in Study IV was to detect the middle childhood origins of later circadian preference. We hypothesized to find some differences in sleep duration or catch-up sleep between the phenotypes, but were unable to detect any. Different aspects of sleep timing were, however, clearly distinguishable between those with preference for eveningness versus those

with preference for morningness already in 8-year-olds. At 8 years of age, weekend sleep timing was different when comparing the different circadian preference groups. 8-year-olds' sleep is commonly still somewhat controlled by parents – this finding highlights the strong individual circadian element in all sleep behaviour. However, as circadian preference has a heritability of up to 50 %, our results may also reflect the circadian preferences of the children's parents. Nevertheless, sleep timing has origins early in life; future research is needed to detect how early on it begins to manifest, and whether interventions may relieve the pressure of health risks related to this phenotype.

8 CONCLUSIONS

There are molecular, behavioural and electrophysiological aspects of sleep that can be measured using various tools. The molecular and electrophysiological levels of sleep occur simultaneously in the brains of the participants while the accelerometers used in these studies measure behavioural aspects of sleep. To what extent these can be detected using measures based on movement, is limited, but is likely to have some associations.

Accelerometer measured sleep seems to have associations with several outcomes. In this thesis, sleep development, cognitive performance and lipid profiles were investigated using actigraphy. While actigraphy is a valid tool for measuring sleep duration and timing, and while it gives an approximation of sleep quality based on the movement the accelerometer detects, it does not provide any information regarding sleep architecture, which measures brain activity during sleep. These measures, especially microstructures in sleep, may reveal critical information regarding the associations between cognitive and/or metabolic processes and sleep, and detect abnormalities stemming from neurodevelopmental disorders or psychopathologies. The technology in sleep medicine is rapidly advancing, so hopefully more lightly administered, holistic options will reach the market within the next few years. Until then, actigraphy remains the best objective tool for epidemiological studies in sleep.

The developmental timeline in this thesis covers the most dynamic period from middle childhood to young adulthood. Regarding sleep studies, this is the period when most of the pathologically significant events occur: sleep and neural development go through vast changes and either support or counter-act each other. During the transition from childhood to adolescence, the brain goes through dramatic changes. Neural development includes prefrontal cortex changes in adolescence, which has an influence on both cognitive performance and sleep. Pubertal development is a marker for neural maturation, but classifications based on physical markers of puberty are not always fine-grained enough to detect the neural level of maturation. Less pronounced effects of sleep on cognition in studies including heterogeneous age distributions may be explained by the variation of neural development.

This thesis has two cross-sectional findings which enlighten the discussion regarding sleep and cognitive domains. In study I, different cognitive domains showed diverse vulnerabilities in association with short or poor sleep. These vulnerabilities were mostly present in boys, which reflects the developmental dimorphisms between girls and boys; testosterone has a greater intensity in the male brain, and it amplifies neural changes up to young adulthood (Paus, 2010). In study III, we found that greater variability

in sleep duration poses a risk for performance-based executive functioning. This is a risk measure often neglected; most recommendations focus on sleep hygiene and duration. Additionally, self-reported executive functioning showed a different association with sleep behaviour than performance based measure: metacognitive index had the most profound association with sleep timing. As metacognitive abilities are also affected by insufficient sleep, cognitive deficits may accumulate without full awareness by the person themselves.

Some aspects of cognition are more stable and resilient against poor sleep. Sleep-related problems relating to cognition may emerge later in development, and then, in older adults, begin to show reciprocal associations such that longer sleep is a symptom of underlying health issues, which then begins to have an association with poorer cognitive performance. Although sleep is time-consuming, it is the price we pay for the brain's plasticity (Tononi & Cirelli, 2014). In order to gain sufficient sleep for optimal cognitive functioning, several aspects of sleep timing and duration need to be optimal. However, in healthy young populations even poor sleep may be sufficient for the time being, and problems may only emerge in later life.

This thesis has two longitudinal findings. In study II we found that lipid profile is more heavily associated with earlier childhood sleep duration and quality than currently occurring sleep. This finding is supported by the molecular mechanisms of lipid metabolism, and also by the potential behaviour and dietary habits sleep deprivation is proven to have. The findings highlight that long-term health consequences of poor sleep may not be immediately evident in healthy populations. Finally, in study IV we were able to detect sleep timing differences already in 8-year-olds among those who, at 17 years of age, report being evening types versus those who report having a morning preference. These findings, too, imply that the importance of sleep timing already in middle childhood needs to be taken in consideration as risks for later circadian preference may be present already at an early age.

The past decades in sleep research have revealed a magnitude of risks and various health outcomes relating to insufficient sleep, late sleep timing. What our findings also suggest is that sleep is both a servant and a slave to self-control. Self-control may be a key in understanding the associations between sleep timing and health, obesity, as well as other metabolic outcomes (Warren et al., 2016).

8.1 FUTURE DIRECTIONS

This thesis suggests that sleep, well-being, and self-control go hand in hand. While our data enabled longitudinal analyses, all results are still only associations and do not infer causality.

Our results may relate to possible reciprocity between sleep timing and self-regulatory skills. Future studies determining the causes for sleep timing, and investigating interventions to control wake-sleep-timing will aid in obtaining sufficient sleep throughout development. Even in healthy populations, the different functions of sleep are more efficiently served when sleep duration, timing, and regularity are respected, especially during critical periods of maturation and neural development, such as in adolescence.

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